Official Protocol Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Determine the Efficacy and Safety of CMB305 in Unresectable Locally-advanced or Metastatic NY-ESO-1+ Synovial Sarcoma Subjects Following First-line Systemic Anti-cancer Therapy
NCT number:	NCT03520959
Document Date:	19-September-2018

CLINICAL TRIAL PROTOCOL: IMDZ-04-1702

Study Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Determine the Efficacy and Safety of CMB305 in Unresectable Locally-advanced or Metastatic NY-ESO-1+ Synovial Sarcoma Subjects Following First-line Systemic Anti-cancer Therapy
Study Number:	IMDZ-04-1702
Study Phase:	3
Product Name:	CMB305 (sequentially administered LV305 [lentiviral vector encoding New York esophageal squamous cell carcinoma-1 {NY-ESO-1} gene] and G305 [NY-ESO-1 recombinant protein plus glucopyranosyl lipid A stable emulsion {GLA-SE}])
IND Number:	16181
Indication:	Unresectable locally-advanced or metastatic synovial sarcoma
Sponsor:	Immune Design Corp. (IMDZ)
Sponsor Address:	IMDZ 1616 Eastlake Ave. E, Suite 310 Seattle, WA 98102 USA
Medical Monitor:	PPD [redacted]

Protocol Date and Version:	19 September 2018, Version 2.1 DK

Confidentiality Statement

SPONSOR'S AND INVESTIGATOR'S SIGNATURE PAGE

Study Number:	IMDZ-04-1702
Product Name(s):	CMB305
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As principal investigator, I agree to:

- Keep all documentation supplied to me or developed by me concerning this study, and that has not been previously published, in the strictest confidence. This documentation includes, but is not limited to, this study protocol, the CMB305 Investigator's Brochure and electronic case report forms (eCRFs). Maintain all information supplied by the sponsor in confidence and, when this information is submitted to an IRB/IEC, ethical review committee, or another group, it will be submitted with a designation that the material is confidential.
- Not commence without prior written approval of a properly constituted institutional review board (IRB) or independent ethics committee (IEC). No changes will be made to the study protocol without prior written approval of Immune Design Corp. (IMDZ) and the IRB/IEC, except where necessary to eliminate an immediate hazard to subjects
- Implement and conduct the study diligently and in strict compliance with the protocol, Good Clinical Practice (GCP), and all applicable laws and regulations.
- Accurately transfer all required data from each subject's source document to the eCRFs. Keep a complete and accurate accounting during and at the completion of the trial of all procedures performed with the drug provided by the sponsor.
- Allow authorized representatives of IMDZ or regulatory authority representatives to conduct on-site visits to review and audit the study documentation. I will personally meet with these representatives at mutually convenient times to answer any trial-related questions.

I have read this protocol and agree to conduct the study as outlined herein, in accordance with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices and comply with the obligations and requirements of clinical investigators and all other requirements listed in 21 Code of Federal Regulations (CFR) Part 312.

Investigator's printed name

Investigator's signature Date (DD/MMM/YYYY)

Institution's name

PPD Medical Monitor

Sponsor's responsible officer

Signature Date (DD/MMM/YYYY)

SYNOPSIS

Sponsor:
Immune Design Corp. (IMDZ)

Name of Finished Product:
CMB305

Name of Active Ingredients:

- LV305 (lentiviral vector [LV] encoding New York esophageal squamous cell carcinoma-1 [NY-ESO-1] gene)
- G305 (NY-ESO-1 recombinant protein plus glucopyranosyl lipid A in stable emulsion [GLA-SE])

Study Title:
A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Determine the Efficacy and Safety of CMB305 in Unresectable Locally-advanced or Metastatic NY-ESO-1+ Synovial Sarcoma Subjects Following First-line Systemic Anti-cancer Therapy

Study Number:
IMDZ-04-1702

Study Phase: 3

Primary Objective:

- Evaluate the efficacy of CMB305 versus placebo using:
  - Progression-free survival (PFS), by investigator assessment, using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
  - Overall survival (OS)

Secondary Objectives:

- Evaluate the efficacy of CMB305 versus placebo using:
  - Time- to-next treatment (TTNT)
  - Distant metastasis-free survival (DMFS)
  - Objective response rate (ORR) (defined by RECIST v1.1)
- Evaluate the safety and tolerability of CMB305 versus placebo
- Evaluate subject quality of life (QoL)

Exploratory Objective:

- Evaluate the anti-NY-ESO-1 immune response and histologic and molecular changes in peripheral blood and tumor tissue and their association with clinical outcomes

Study Design:
This is a global, randomized, double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of the CMB305 vaccine regimen versus placebo in subjects with synovial sarcoma expressing NY-ESO-1.

To be eligible, subjects must be receiving a first-line systemic anti-cancer therapy for unresectable locally-advanced or metastatic synovial sarcoma and have no evidence of progression at the time of randomization.

The study will consist of 5 periods: Pre-screening, Screening, Treatment, Post-treatment, and Long-term Follow-up.

The schedule of events is presented in Table 1 for the Pre-Screening and Screening periods and in Table 2 for the Treatment through the Long-term Follow-up periods. Study flow diagrams for subjects who received either a course of 4 cycles, 6 cycles, or 8 cycles of first-line systemic anti-cancer therapy are presented in Appendix 5, Figure 4, Figure 5 or Figure 6, respectively. A study flow diagram for subjects who have had local regional therapy after first-line systemic anti-cancer therapy is presented in Appendix 5, Figure 7.

Pre-screening period:

The Pre-screening period of up to 151 days (Day -180 to Day -29) commences at the time the subject and/or their legally authorized representative sign the Pre-screening informed consent form (ICF)/assent form. The Pre-screening period ends at the time the subject and/or their legally authorized representative sign the Main Study ICF/assent form.

Before any Pre-screening procedures are performed, subjects aged ≥18 years or legally authorized representatives of subjects <18 years will provide written consent on the Pre-screening ICF, and subjects aged 12 to <18 years will provide written assent. At the time of Pre-screening, subjects must still be receiving treatment with first-line systemic anti-cancer therapy. The following will be evaluated during the Pre-screening visit:

- Radiographic disease response assessment obtained at the standard-of-care time point by the investigator using RECIST v1.1
- Immunohistochemistry (IHC) test for the presence of NY-ESO-1 in an archival tumor tissue or fresh tumor tissue biopsy (tumor tissue may be from an archived sample obtained within 18 months before signing the Pre-screening ICF/assent form)

Once the investigator confirms 1) the subject has no evidence of progression (using RECIST v1.1) and 2) the IHC test results for NY-ESO-1 are positive (≥1% expression), then the subject and/or their legally authorized representative will sign the Main Study ICF/assent form.

Screening period:

The duration of the Screening period of up to 28 days (Day -28 to Day -1) and begins on the date the subject and/or their legally authorized representative sign the Main Study ICF/assent form and ends at time of randomization.

After satisfying the Pre-screening criteria, subjects aged ≥18 years and legally authorized representatives of subjects <18 years will provide written consent on the Main Study ICF, and subjects aged 12 to <18 years will provide written assent for study participation. Once the appropriate Main Study ICF/assent form is signed, subjects will undergo additional eligibility assessments and the investigator will confirm there is no evidence of progression (using RECIST v1.1). The disease status will be assessed by the investigator (using RECIST v1.1) through comparison of the most recent baseline images obtained during Screening to both 1) the images obtained prior to initiation of first-line systemic anti-cancer therapy and 2) the images obtained per standard-of-care during first-line systemic anti-cancer therapy to confirm there is no evidence of progression prior to randomization. Investigator assessment of radiographic images confirming best response (stable disease [SD] or better) to first-line systemic anti-cancer therapy using RECIST v1.1 will be entered into an electronic case report form (eCRF). Subjects who have a tumor response of SD with evidence of ≥15% to 20% increase in tumor burden will be submitted for Central Review to adjudicate the investigator's assessment of tumor response prior to randomization. Radiographic images from both Screening and Pre-Screening will also be submitted to an independent review committee (IRC) for storage. The stored images will be available for evaluation by a central reader, if requested by the sponsor. After completion of Screening assessments and confirmation that the subject has met all eligibility requirements, the subject will be randomly assigned to one of the treatment arms using a central randomization system on Day 1.

Treatment period:

The Treatment period will begin on the day of randomization (Day 1), which is to be within 28 days after the last dose of first-line systemic anti-cancer therapy or the last day of local regional therapy, if applicable, and will continue until investigator-determined progressive disease (PD) (using RECIST v1.1), unacceptable toxicity, or 1 year after the first dose, whichever occurs first.

Subjects who meet eligibility criteria will be randomly assigned in a 1:1 ratio to receive one of the following centrally randomized treatments:

- Arm A: Placebo
- Arm B: CMB305

An interactive response technology (IRT) system will use the following stratification factors at the time of randomization:

- Disease status at screening: locally advanced unresectable (LAUR) vs metastatic
- Tumor response during screening: stable disease (SD)/partial response (PR) vs complete response (CR)/no evidence of disease (NED)
- Baseline presence of anti-NY-ESO-1 antibody (yes vs no)

Subjects who are randomly allocated to the placebo arm will not be permitted to cross-over to the CMB305-containing treatment arm at any time before study closure.

Tumor imaging assessments will be performed every 8 weeks after Day 1 and radiographic evidence of disease progression will be determined by the investigator using RECIST v1.1. Subjects with a global deterioration of health status requiring discontinuation of study treatment but without objective evidence of disease progression (symptomatic deterioration) will be considered as having PD for the purpose of determining PFS. Radiographic images (e.g., computed tomography [CT] scan or magnetic resonance imaging [MRI]) will also be submitted to an independent review committee (IRC) for storage and will be available for evaluation by a central reader, if requested by the sponsor. Details for the collection and evaluation of radiographic images are included in the Radiology Manual provided to the study sites.

Tumor biopsy samples for NY-ESO-1 expression will be obtained from all subjects during the Pre-screening period (either archival tumor tissue or a fresh biopsy sample). All subjects will provide peripheral blood samples for anti-NY-ESO-1 antibody assay for stratification during screening.

Quality of life will be assessed up to 12 months from Day 1.

Safety will be monitored by evaluating the frequency and severity of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, immunogenicity, and persistence. Local laboratory test values will be used for treatment decisions and subject care; central laboratory test values will be used in the analysis of safety.

In addition, at only select US sites, the following will be collected:

Peripheral blood samples for the anti-NY-ESO-1 T cell and antibody assays will be obtained prior to start of study treatment from subjects on Day 1, Day 92, and Day 365 for subjects who have not had a progression event. A tumor biopsy will be obtained at screening, Day 92, and Day 365 for subjects who have not had a progression event. An additional tumor biopsy at time of progression event will be encouraged.

Post-treatment period (for subjects who discontinue study treatment for reasons other than disease progression):

The Post-treatment period will begin at the end of treatment and will continue until investigator-determined radiographic PD (using RECIST v1.1) is documented.

Subjects will continue to undergo imaging until the time of disease progression. At the time of disease progression, subjects will enter the Long-term Follow-up period.

Long-term Follow-up period:

The Long-term Follow-up period will begin at the time investigator-determined PD (using RECIST v1.1) is documented and will continue for up to 5 years, until the date of death, or until sponsor notification of study closure.

Study Population:

Approximately 248 subjects who have synovial sarcoma expressing NY-ESO-1 will be enrolled and randomly assigned in a 1:1 ratio to treatment with CMB305 or placebo.

Inclusion Criteria:

1. Have documented histologic diagnosis of synovial sarcoma (may be confirmed by the presence of t(X;18) (p11:q11) translocation or B cell lymphoma 6 corepressor [BCOR] rearrangement) and have disease that is unresectable locally-advanced or metastatic prior to the start of first-line systemic anti-cancer therapy. Unresectable is defined as having evidence of positive surgical margins after resection of primary disease or a documented surgical consultation with assessment of an inability of resection to provide clear margins.
2. Have IHC test results from tumor biopsy for NY-ESO-1 that are positive (≥1% expression).
3. At the time of Pre-screening, subjects must be receiving a first-line anthracycline or ifosfamide-containing systemic anti-cancer therapy regimen (single agent ifosfamide, single agent anthracycline, combination anthracycline plus ifosfamide, or combination anthracycline plus olaratumab). Subjects must have received at least 4 cycles but no more than 8 cycles of therapy (or no more than 180 days of systemic anti-cancer therapy). Subjects who have received local regional therapy (surgical resection, radiotherapy, radiofrequency ablation, or cryotherapy) are eligible if they meet the following:
    a. Subjects whose disease converted to operable after completion of first-line chemotherapy are eligible, if local regional therapy (surgical resection, radiotherapy, radiofrequency ablation or cryotherapy) is completed within the 180-day period from the date of the first dose of first-line systemic anti-cancer therapy. Please note that an extension of this 180-day may be allowed per Section 3.3 of the protocol.
    b. Subjects whose disease remains inoperable after completion are eligible, if radiotherapy is completed within the 180-day period from the date of the first dose of first-line systemic anti-cancer therapy and there is no evidence of progressive disease prior to initiation of radiotherapy. Please note that an extension of this 180-day period may be allowed per Section 3.3 of the protocol.
    c. Subjects who have PD ≤6 months after date of last dose of adjuvant/neoadjuvant systemic anti-cancer therapy or date of last day of local regional therapy are not eligible.
4. Must have documentation of no evidence of disease progression of the tumor during or after completion of first line systemic anti-cancer therapy as determined by the investigator using RECIST v1.1 guidelines. Subjects who have a tumor response of SD with evidence of ≥15% to 20% increase in tumor burden will be submitted for Central Review to adjudicate the investigator's assessment of tumor response prior to randomization. Subjects with NED are eligible.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Age ≥12 years.
7. Have a life expectancy of at least 6 months, as determined by the investigator.
8. If a female of child-bearing potential (FCBP), willing to undergo pregnancy testing and agree to use at least 1 highly-effective contraceptive method; such methods include combined

estrogen and progesterone-containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), or progesterone only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner or true sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject, refraining from heterosexual intercourse during the entire period of risk associated with study treatments) during the dosing period and for 1 month (which is the duration of a menstruation cycle) after administration of the last dose of CMB305. More stringent contraception criteria should be followed if requested by local regulatory authorities.

9. If male and sexually active with a FCBP, must be surgically sterile (i.e., vasectomy) or agree to use highly-effective contraception, such as latex condom, during the dosing period and for 3 months (which is the duration of a sperm cycle) after administration of the last dose of CMB305. More stringent contraception criteria should be followed if requested by local regulatory authorities.
10. Have recovered from the toxic effects (except alopecia) to grade 2 or better from systemic anti-cancer therapy according the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 (or newer).

Exclusion Criteria:

1. Have received the last dose of first-line systemic anti-cancer therapy or date of most recent local regional therapy >28 days prior to Day 1.
2. Have received prior anti-NY-ESO-1 therapy.
3. Have received first-line systemic anti-cancer therapy other than an anthracycline-containing or ifosfamide-containing regimen (single agent anthracycline, single agent ifosfamide, combination anthracycline plus ifosfamide, or combination anthracycline plus olaratumab).
4. Have received treatment with systemic immunomodulatory agents (including, but not limited to, interleukin-2) within 28 days prior to administration of the first dose of CMB305 (i.e., Day 1) or 5 half-lives of the drug, whichever occurs sooner.
5. Have significant immunosuppression from:
   a. Concurrent, recent (≤21 days prior to administration of the first CMB305 dose [i.e., Day 1]), or anticipated need for chronic treatment with systemic immunosuppressive dose of corticosteroids (the use of physiologic doses of corticosteroids may be approved after consultation with the sponsor). The use of topical or inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.
   b. Other immunosuppressive medications (≤21 days prior to administration of the first CMB305 dose [i.e., Day 1]) including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor (anti-TNF) agents or conditions such as common variable hypogammaglobinemia.
6. Have psychiatric, other medical illness, or any other condition that, in the opinion of the investigator, prevents compliance with the study procedures or the ability to provide valid informed consent (or assent for subjects 12 to <18 years of age).
7. Have a history of uncontrolled autoimmune disease. Uncontrolled disease is defined as one requiring chronic supra-physiologic doses of systemic steroids or other forms of immunosuppression or that requires a recently increased or newly prescribed dose within 28 days of Screening.
8. Have significant electrocardiogram (ECG) finding or cardiovascular disease, such as New York Heart Association cardiac disease (>Class II), myocardial infarction within the previous

3 months before administration of the first dose of CMB305 (i.e., Day 1), unstable arrhythmias, or unstable angina.

9. Have inadequate organ function as evidenced by:
   a. Marrow:
      i. Absolute neutrophil count (ANC) ≤1000/mm^3
      ii. Platelets <75,000/mm^3
      iii. Hemoglobin (Hgb) <8 g/dL
      iv. Lymphocytes ≤800/mm^3.
   b. Hepatic:
      i. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0× the upper limit of normal (ULN) for subjects without liver metastases **or** ≥5× ULN for subjects with liver metastases
      ii. Total serum bilirubin >1.5× ULN (**or** direct bilirubin ≥1.5 ULN for subjects with total bilirubin levels <1.5× ULN). Subjects with Gilbert's disease may be included if their total bilirubin is <3.0 mg/dL).
   c. Renal:
      i. Creatinine clearance <0.5 x LLN.
   d. For subjects not using blood thinners:
      i. Prothrombin time (PT) >1.5× ULN or international normalized ratio (INR) >1.5× ULN
      ii. Partial thromboplastin time (PTT) >1.5× ULN
      iii. Subjects using blood thinners must be able to modify their normal dosing regimen to allow for injections of investigational product.
10. History of other cancer within 3 years (except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, localized prostate cancer treated with curative intent, ductal carcinoma in situ treated surgically with curative intent, or other cancers with a similar outcome).
11. Evidence of active tuberculosis or recent (<1 week prior to first scheduled dosing on Day 1) clinically-significant infection requiring systemic therapy. (Prophylactic antibiotics [e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease] are permitted.)
12. Evidence of active hepatitis B (HepB), hepatitis C (HepC), or human immunodeficiency virus (HIV) infection:
    a. Active HepB is defined as having a positive HepB surface antigen (HBsAg) test result at Screening.
    b. Subjects with past/resolved HepB infection (defined as having a negative HBsAg test and a positive antibody to HepB core antigen [anti-HBc] antibody test) are eligible. HepB viral DNA results must be negative in these subjects prior to the first scheduled dosing on Day 1.
    c. Subjects with test results positive for HepC antibody are eligible only if polymerase chain reaction (PCR) testing is negative for HepC viral RNA.
    d. Subjects who are HIV positive.
13. Have had live, attenuated vaccine administered within 28 days prior to the first scheduled dosing on Day 1 or anticipate that such a live, attenuated vaccine will be required during the study.
14. Have a history of brain metastasis.

15. Have received cancer therapies, including chemotherapy, radiation, biologic or kinase inhibitors, granulocyte colony-stimulating factor (G-CSF), or granulocyte-macrophage colony stimulating factor (GM-CSF) within 3 weeks prior to the first scheduled CMB305 dosing.
16. A FCBP who is pregnant, is planning to become pregnant, or is breast feeding; or a male who is sexually active with a FCBP who is planning to become pregnant.
17. Hypersensitivity to an ingredient of either LV305 or G305

Reference Product, Dose, and Mode of Administration:

Arm A:

- Matching placebo for LV305 will be normal saline and will be administered subcutaneously (SC) on Days 1, 22, 50, and 78.
- Matching placebo for G305 will be administered intramuscularly (IM) on Days 36, 64, 92, and then at 8-week intervals up to 1 year or until investigator-determined PD (using RECIST v1.1) is documented or unacceptable toxicity, whichever occurs first. The G305 placebo will have 2 components:
  - Matching placebo for the NY-ESO-1 component of G305 will be normal saline
  - Matching placebo for the GLA-SE component of G305 will be the non-active stable emulsion (SE)

Test Product, Dose, and Mode of Administration:

Arm B: CMB305 (sequentially administered LV305 and G305)

- LV305 at a dose of 4×10^{10} vector genomes (vg) will be administered SC on Days 1, 22, 50, and 78.
- G305 is composed of 5 µg GLA-SE admixed with 250 µg of NY-ESO-1 protein. G305 will be administered IM on Days 36, 64, 92, and then at 8-week intervals up to 1 year or until investigator-determined PD (using RECIST v1.1) is documented or unacceptable toxicity, whichever occurs first.

Duration of Treatment:

Subjects in Arm A will receive placebo according to the same schedule for CMB305 for up to 1 year after Day 1 or until investigator-determined PD (using RECIST v1.1) is documented or the occurrence of unacceptable toxicity, whichever occurs first.

Subjects in Arm B will receive CMB305 induction through Day 92 and then booster vaccines at 8-week intervals up to 1 year after Day 1 or until investigator-determined PD (using RECIST v1.1) is documented or the occurrence of unacceptable toxicity, whichever occurs first.

Efficacy Assessments:

Primary:

- PFS, by investigator assessment, using RECIST v1.1
- OS

Secondary:

- TTNT
- DMFS
- ORR (defined by RECIST v1.1)
- Safety and tolerability
- QoL evaluated using the EuroQol 5-Dimension 5 Level (EQ-5D-5L) for subjects ≥18 years of age or using the EuroQol 5-Dimension Youth (EQ-5D-Y) for subjects 12 to <18 years of age

Exploratory:

- Intratumoral and peripheral blood anti-NY-ESO-1 immune changes

Safety Assessments:

- The nature, frequency, and severity of AEs and SAEs
- Clinical laboratory parameters (hematology, chemistry, and urinalysis), as measured by the central laboratory
- Vital sign measurements (blood pressure, heart rate, temperature, and respiratory rate)

Statistical Methods:

Multiple Comparisons:

The study is to be conducted with PFS and OS as 2 primary endpoints with the goal to support regulatory approval based on PFS or OS. The overall type I error probability is specified to be 1-sided 0.025 with success for either 1 of the 2 primary endpoints defining study success using the Bonferroni method to specify that each endpoint will be evaluated using a type I error probability of 1-sided 0.0125 to protect the overall type I error probability.

Sample Size Calculation:

A total of 248 subjects will be randomly allocated in a 1:1 ratio such that 124 subjects will be in each of the 2 treatment arms. The study is powered at 90% with 179 death events required to detect a hazard ratio (HR) of 0.59, which corresponds to a 41% reduction in the risk of death, and an approximately 69% increase in median survival compared with placebo median survival of 20 months, and uses a 1-sided log-rank test, with an alpha of 0.0125, a 1:1 randomization ratio, and an interim OS non-binding futility analysis with the boundary HR = 1.0 at 67% of information time (120 death events from the 179 required death events for the final OS analysis). A total of 248 subjects will yield the 179 events required, under the assumption of 24 months for enrollment (25% of subjects enrolled in the first year and 75% of subjects enrolled in the second year) plus 42 additional months for follow-up.

With 141 PFS events, the study is powered at 90% to detect a HR of 0.55, which corresponds to a 45% reduction in the risk of PFS events (either disease progression or death), and an approximately 82% increase in median PFS compared with the placebo median PFS of 4 months, and uses a 1-sided log-rank test, with an alpha of 0.0125, and a 1:1 randomization ratio.

Analysis Sets:

For the purpose of statistical analysis, there are 3 analysis sets: Intent-to-Treat set (ITT), Efficacy Evaluable set (EE), and Safety set.

- The ITT set consists of all subjects randomized. All analyses of this set will be based on the randomized treatment arm to which the subjects are assigned. Efficacy analyses performed on the ITT set will be considered to be the primary indicator of efficacy.
- The EE set consists of all subjects without major protocol violations, who have received at least 1 dose of study drug, and have the baseline and at least 1 post-baseline tumor assessment available. The EE set will be analyzed according to the treatment received. Efficacy analyses performed in the EE set will be considered to be supportive.
- The Safety set consists of all subjects taking any amount of study drug. The Safety set is the primary set for safety analyses including AEs and clinical laboratory data. Study treatment exposure also will be summarized using the Safety set. Analyses performed in the Safety set will be considered to be supportive.

Primary Efficacy Analyses:

The 2 primary efficacy endpoints of PFS and OS will be compared between CMB305 and placebo. OS is defined as the time from randomization to the date of death. PFS by investigator's assessment is defined as the time from randomization to the investigator-determined (using RECIST v1.1) date of disease progression or death. Radiographic images will be collected and assessed using RECIST v1.1 until the time the subject begins a new line of treatment.

For the purpose of the PFS analysis, any one of the following events, whichever occurs first, will be used:

- Disease progression per RECIST v1.1 (See Appendix 1, Table 7 [Eisenhauer 2009])
- Symptomatic deterioration (global health deterioration) as described by RECIST v1.1
- For subjects with NED at the time of randomization, any new malignant lesion that occurs after randomization per RECIST v1.1 (See Appendix 1, Table 8.)

Otherwise, subjects who do not have disease progression or have not died will be censored at the date when the last tumor imaging assessment determines a lack of progression. If a subject begins a new anti-cancer therapy or has radiotherapy, surgery, or other local regional therapy at a lesion site prior to documented progression, the subject will be censored at the last assessment where the subject was documented as progression free prior to the intervention. Subjects with 2 or more missing response assessments (except for subjects with symptomatic deterioration) prior to a visit with documented progression (or death) will be censored at the last visit where the subject was documented to be progression free. Progression-free survival by investigator's assessment, will be the primary PFS analysis. Progression-free survival by independent radiological review will be the supportive analysis.

The null hypothesis, which is that there is no difference in OS/PFS between CMB305 and placebo, will be tested using a stratified log-rank test stratified by: disease status at screening (locally advanced unresectable versus metastatic), tumor response during screening (PR/SD versus CR/NED) and baseline presence of anti-NY-ESO-1 antibody (yes versus no).

The null hypothesis will be rejected, and it will be concluded that OS/PFS on CMB305 is superior to that on placebo in subjects with synovial sarcoma if the 1-sided p value at the final analysis for the stratified log-rank test is less than the pre-specified alpha of 0.0125 as discussed above in the Multiple Comparisons section. The associated HR and its 2-sided 97.5% and 95% confidence interval (CI) will be provided using the stratified Cox proportional hazard model. The Kaplan-Meier curve will summarize OS/PFS graphically by treatment arm. Tabular summaries of the Kaplan-Meier curves, including the median, will be provided by treatment. The 1-year and 18-month OS/PFS rate will be

provided by treatment. The final PFS analysis will be conducted when a total of 141 PFS events occur. The final OS analysis will be conducted when a total of 179 deaths occur.

Secondary Efficacy Analyses:

The secondary efficacy endpoints of TTNT, DMFS, ORR, and QoL using the EQ-5D-5L or EQ-5D-Y will be compared between treatment arms.

The secondary efficacy endpoints will only be evaluated if at least 1 of the 2 primary efficacy endpoints demonstrate superiority for CMB305 over placebo. Furthermore, to control the overall family-wise Type I error rate at 1-sided $\alpha = 0.025$ for the secondary efficacy endpoints, the secondary efficacy endpoint of TTNT will be tested first at 1-sided alpha of 0.025. DMFS will be tested at 1-sided alpha of 0.025 only if TTNT shows significant improvement.

Exploratory Analyses:

The baseline anti-NY-ESO-1 immune response and histologic and molecular changes in peripheral blood and tumor tissue and their association with clinical outcomes will be explored. In addition, a relationship between an induced anti-NY-ESO-1 immune response as well as tumor tissue changes during study treatment and clinical outcomes will be evaluated using peripheral blood and tumor tissue biopsies collected during study treatment at select sites.

Safety Analyses:

Safety will be assessed primarily based on reported AEs. A treatment-emergent adverse event (TEAE) is an AE with an onset on or after the initiation of study treatment, or a pre-existing condition that worsens after initiation of study treatment (i.e., increase in severity). Medical events of interest, immune-mediated events and AEs that occur more than 30 days after the last dose, and that are deemed as related to the study drug will be included as TEAEs. TEAEs occurring from the time of the first dose through 30 days after the last dose of the study drug and medical events of interest, immune-mediated events and related AEs will be summarized. All AEs will be coded using the Medical Dictionary for Regulatory Affairs® (MedDRA v20.0 or newer). TEAEs will be tabulated by system organ class, preferred term, treatment, and will be further categorized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE [v4.03 or newer]) grade, and by relationship to the study drug. Clinically significant laboratory abnormalities will be reported as AEs. The incidence of each AE will be provided as the total number of subjects that experience the AE, as well as the percentage of the population that this represents. If an AE is reported more than once during treatment for a given subject, the worst grade of severity and the most conservative relationship will be presented in the summary tables.

AEs will also be listed for individual subjects, along with information regarding onset, duration, grade, relationship to the study drug, and outcome. AEs that lead to withdrawal from study treatment will be listed and summarized. Tabulations and listings of SAEs and deaths will also be generated.

It is the responsibility of the investigator to assess the clinical significance of all abnormal values obtained from the local laboratory as defined by the list of reference ranges from the investigational site local laboratory. In some cases, significant changes in local laboratory values within the normal range will require similar judgment. An abnormal laboratory value performed by the local laboratory that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- An action on the study drug is made as a result of the abnormality
- Intervention for management of the abnormality is required
- At the discretion of the investigator should the abnormality be deemed clinically significant

Data Monitoring Committee and Interim Analysis:

A data monitoring committee (DMC) will be established with the responsibility of safeguarding the interest of study subjects and maintaining the overall integrity of the study. The DMC will review safety data periodically during the study and will evaluate the results of final PFS analysis and a planned interim OS analysis to assess futility with the possibility of a recommendation for stopping the study early because of futility. The OS non-binding futility boundary is set to be HR=1.0. It will be conducted at 67% of information time (120th death event from the 179 required death events for final OS analysis). If deemed necessary by the DMC, unblinded data may be reviewed on a case-by-case basis. The sponsor will remain blinded to study treatment until either 1 of the 2 primary endpoints is met or until the study has been stopped early. Details of the DMC function will be governed by a DMC Charter developed by the sponsor and accepted by DMC members.

Date of Original Approved Protocol: 30 January 2018

Date of Most Recent Protocol Amendment (if applicable): 19 September 2018

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PROTOCOL REVISION HISTORY

Version	Date	Comment
00	16 November 2017	Initial Release
1.0	30 January 2018	IMDZ has revised the protocol to call PFS and OS the "two primary endpoints" for this study. Revisions were made to the Study Synopsis on Page 10, 11, 12, and 13; Section 7.4, Primary Endpoints on Page 69; Section 7.7.1, Primary Efficacy Analyses on Page 69; Section 7.7.2, Secondary Efficacy Endpoints on Page 70; Section 7.10, Multiplicity on Page 72; and Section 7.11, Data Monitoring Committee and Interim Analysis on Page 72. IMDZ has revised the protocol to state that the efficacy analysis performed on the ITT set will be the primary indicator of efficacy, and the efficacy analyses performed on the EE and Safety sets will be supportive. Revisions were made to the Study Synopsis on Page 11 and to Section 7.2 Analysis Sets on Page 68. Additional revisions made for clarity and consistency
2.0	27 April 2018	The main revisions completed in Version 2.0 of the study protocol are the following: 1. Updated and clarified study stratification factors at the time of randomization 2. Updated Inclusion Criteria to clarify eligibility of subjects who have received first-line systemic anti-cancer therapy 3. Updated Exclusion Criteria to specify which anthracycline-containing and ifosfamide-containing regimens are allowed 4. Clarified language regarding collection of plasma for immune response assessment and potential exploratory biomarkers for CMB305 immunogenicity 5. Included conduct of a pre-specified sensitivity analysis based on the number of cycles and type of prior therapy (neoadjuvant/adjuvant chemotherapy and surgery and/or radiotherapy) 6. Added Treatment Modification and Discontinuation Section (Section 5.6) 7. Clarified that treatment modifications (dose reductions or increases) will not be permitted as a result of DMC reviews.
2.1 DK	19 September 2018	The main revisions completed in Version 2.1 DK of the study protocol: 1. Section 4.2 Inclusion Criteria and Section 6.4.8: Updated and clarified to contraceptive advice with 'highly affective' and 'true sexual abstinence' 2. Section 5.5 Blinding: Updated that in emergency situations, the responsibility to break the treatment code resides solely with the investigator 3. Section 1.1.2 added language for C131 Arm E clearing the safety period for higher dose of LV305 4. Synopsis and Section 4.3 Exclusion: "17. Hypersensitivity to an ingredient of either LV305 or G305"

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	antibody to hepatitis B core antigen
anti-TNF	anti-tumor necrosis factor
AST	aspartate aminotransferase
BCOR	B cell lymphoma 6 corepressor rearrangement
CFR	Code of Federal Regulations
CI	confidence interval
CR	complete response
CT	computed tomography
DC	dendritic cell
DC-SIGN	dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin receptor (CD209)
DMC	data monitoring committee
DMFS	distant metastasis-free survival
DMPC	dimyristoylphosphatidylcholine
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EE	Efficacy Evaluable
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
EQ-5D-5L	EuroQol 5-Dimension 5-Level
EQ-5D-Y	EuroQol 5-Dimension Youth
ESMO	European Society for Medical Oncology
FCBP	female of child-bearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GLA	glucopyranosyl lipid A
GLA-SE	glucopyranosyl lipid A stable emulsion
GLP	Good Laboratory Practice
GM-CSR	granulocyte-macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
HbsAg	hepatitis B surface antigen
HEENT	head, eyes, ears, nose, and throat
HepB	hepatitis B

HepC	hepatitis C
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IHC	immunohistochemistry
IM	intramuscular(ly)
IMDZ	Immune Design Corp.
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
LV	lentiviral vector
MedDRA	Medical Dictionary for Regulatory Affairs
MEOI	medical event of interest
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NED	no evidence of disease
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NY-ESO-1	New York esophageal squamous cell carcinoma-1
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
Rev	Regulator of Expression of Virion Proteins (lentivirus accessory protein)
RR	response rate

SAE	serious adverse event
SC	subcutaneous(ly)
SD	stable disease
SE	stable emulsion
SINV	Sindbis virus
SINVar1	Sindbis virus envelope glycoprotein
STS	soft tissue sarcoma
TEAE	treatment-emergent adverse event
TLR4	toll-like receptor 4
TTNT	time-to-next treatment
ULN	upper limit of normal
US	United States
vg	vector genome
WHO	World Health Organization

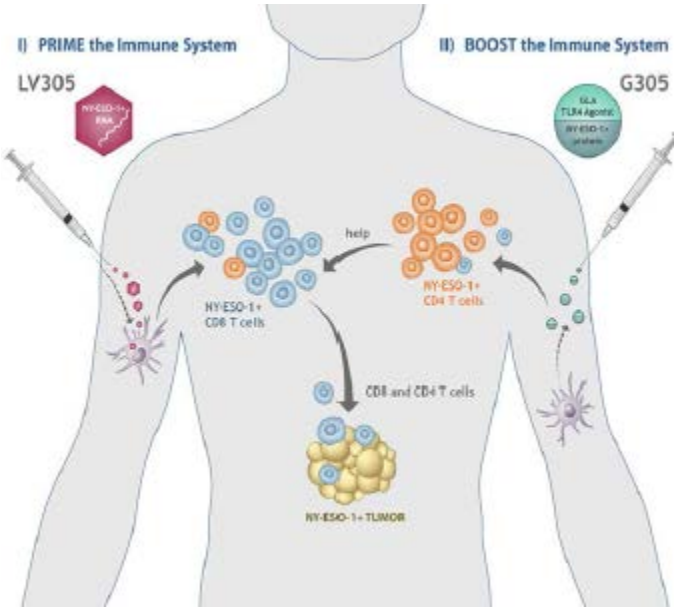
1.0 INTRODUCTION

1.1 Background

1.1.1 CMB305 Is a "Prime-boost" Immunotherapy Targeting NY-ESO-1

Immune Design Corp. (IMDZ) is developing a first-in-class in vivo dendritic cell (DC)- targeting active immunotherapy, designated as CMB305 and shown in Figure 1, which combines 2 different safe and active immunotherapy products administered sequentially in a "prime-boost" vaccination regimen to maximize the immune response against NY-ESO-1. One product is LV305, a lentiviral vector (LV) derived from the ZVex platform that encodes the NY-ESO-1 cancer testes antigen and is designed to "prime" the immune system by targeting RNA antigen delivery to DCs in vivo. The other product is G305, an immune system "boost" component, which is a recombinant NY-ESO-1 protein admixed with the adjuvant glucopyranosyl lipid A stable emulsion (GLA-SE), an agonist of toll-like receptor 4 (TLR4) that is highly expressed on DCs. The tumor antigen targeted by the CMB305 regimen is the cancer testes antigen, NY-ESO-1, which is virtually absent in healthy tissues, but is expressed in many tumor types and often associated with a worse prognosis (Gnjatic 2006; Nicholaou 2006; Jungbluth 2001a; Komarov 2017).

Figure 1 CMB305 Prime/Boost Regimen



Each LV305 dose = 4×10^{10} vg; each G305 dose = 5 µg dose of GLA plus 250 µg of NY-ESO-1 protein.

Development of CMB305 addresses multiple shortcomings of prior cancer vaccines including vaccines targeting DCs ex vivo (Sabado 2017; Anguille 2014). The CMB305 mechanism of action is based on the selective in vivo targeting of DCs (LV305) to generate killer T cells and the generation of CD4 T cell "help" by the "boost" component, G305, to induce a broad and

long-lasting adaptive anti-NY-ESO-1 immune response involving CD8+ and CD4+ T cells and antibodies, as well as other effector immune cells. CMB305-induced anti-NY-ESO-1 immune responses become detectable mainly during the third month of administration.

Compared with other vectors previously used for immunization, such as adenovirus or vaccinia, LV305 selectively transduces the NY-ESO-1 RNA antigen to DCs, is replication-incompetent, which minimizes inflammation, and selectively activates the transduced DC to enhance its antigen presentation capabilities (Butler 2011). These attributes of LV305 contribute to its favorable safety profile and its association with potentially superior and long-term memory anti-NY-ESO-1 immune responses.

1.1.2 Overview of Data Generated from Initial Clinical Development of CMB305

Individual components of the CMB305 regimen, LV305 and G305, were first evaluated in separate phase 1 studies, followed by a phase 1 study of the CMB305 regimen:

- **ID-LV305-2013-001** is a phase 1, open-label study designed to evaluate the safety, tolerability, and immunogenicity of intradermally (ID) administered LV305 in subjects with locally-advanced, relapsed, or metastatic cancer expressing NY-ESO-1
- **G305/IDC-G305-2013-001** is a phase 1, open-label, multiple ascending dose study evaluating the safety, tolerability, and immunogenicity of the intramuscular (IM) NY-ESO-1 protein with GLA-SE adjuvant in subjects with unresectable or metastatic cancer expressing NY-ESO-1
- **IMDZ-C131** is a phase 1, open-label study designed to evaluate the safety, tolerability, and immunogenicity of ID or subcutaneously (SC) administered CMB305 in subjects with locally-advanced, relapsed, or metastatic cancer expressing NY-ESO-1

Based on the mechanism of action, rapid tumor shrinkage is not expected from CMB305 therapy, and clinical benefit should be assessed beyond disease progression as determined by conventional RECIST. Thus, CMB305 clinical development is focused on understanding long-term benefit including overall survival (OS) in the early clinical studies.

While subjects with different NY-ESO-1+ solid tumors including several types of soft tissue sarcoma (STS) have been enrolled in the LV305-2013-001 and IMDZ-C131 clinical studies, subjects with synovial sarcoma emerged as the primary focus of clinical development due to the uniformly high expression level of NY-ESO-1 in these tumors. Thirty-four NY-ESO-1+ subjects with synovial sarcoma were treated on studies LV305-2013-001 and IMDZ-C131. The vast majority of subjects with synovial sarcoma in both studies received prior systemic chemotherapy, had metastatic disease, and a high level of NY-ESO-1 expression by immunohistochemistry (IHC) (Somaiah 2017a; Somaiah 2017b), which is associated with a worse prognosis (Nicholaou 2006; Jungbluth 2001a; Van Tine 2016; Komarov 2017).

Induction of anti-NY-ESO-1 immune response is an important pharmacodynamic marker of activity for LV305 and CMB305, and possibly a predictive marker of a better clinical outcome. LV305 and CMB305 resulted in anti-NY-ESO-1 immune responses and extended tumor growth stabilization in subjects with NY-ESO-1+ sarcoma. However, CMB305 induced stronger and broader immune responses than LV305 alone such as: stronger T cell responses in each ELISPOT, in more samples per subject and in more subjects; induction of anti-NY-ESO-1 antibodies (not observed with LV305); and antigen spreading in more than 35% of subjects versus less than 20% of subjects who were treated with LV305. Other NY-ESO-1 vaccine trials reported an association of (1) induction of anti-NY-ESO-1 immune responses with improved survival in subjects with ovarian cancer and melanoma (Szender 2017; Odunsi 2012), and (2) integrated anti-NY-ESO-1 immune responses with survival in subjects with melanoma (Yuan 2011).

Safety has been established for two dose levels of LV305 (1×10^{10} vector genomes (vg)/mL and 4×10^{10} vg/mL) in combination with G305 (5 µg GLA-SE plus 250 µg NY-ESO-1 protein) in the previous IMDZ-C131 study. In the IMDZ-C131 study, the dose of the LV305 component of CMB305 was increased from 1×10^{10} vg to 4×10^{10} vg (1×10^{10} vg single injection in each upper extremity and each lower extremity, total 4 injections administered subcutaneously). The G305 dose is unchanged (5 µg GLA-SE plus 250 µg NY-ESO-1 protein). This increase in LV305 dose is being implemented to maximize potential clinical benefit of CMB305 without compromising safety.

The dose at $4x10^{10}$ vector genomes has been evaluated in Arm E of IMDZ-C131. Nine subjects with soft tissue sarcoma were evaluated at this higher dose of LV305. No Serious Adverse Events, Medical Events of Interest, or Dose-Limiting Toxicities were reported. The data were reviewed by the Data Monitoring Committee (DMC) and this Committee regarded LV305 to be well tolerated and to continue the study at the (4×10^{10} vg/mL) and G305 (5 µg GLA-SE plus 250 µg NY-ESO-1 protein).

Data for each component, LV305 and CMB305, are discussed because the LV305 component is essential for priming the anti-NY-ESO-1 immune response in subjects receiving the CMB305 regimen. Long-term follow-up approaching 24 and 12 months for studies LV305-2013-001 and IMDZ-C131, respectively, indicate that LV305 and CMB305 therapy may lead to a substantial improvement in OS in subjects with NY-ESO-1+ synovial sarcoma who received multiple prior therapies compared with the published survival data. For subjects with synovial sarcoma enrolled in the LV305-2013-001 study, median OS has not yet been reached; and for the IMDZ-C131 study, median OS is 19.3 months. The 12-month OS rate is 84% and 73%, and the 18-month OS rate is 76% and 55% on LV305-2013-001 study and IMDZ-C131 study, respectively (Somaiah 2017a). Overall, OS for subjects with NY-ESO-1+ STS, including those with synovial sarcoma on LV305 and CMB305 therapy, compares favorably with currently approved agents for recurrent STS where OS ranges from 12.4 to 13.5 months, and, more specifically, for metastatic synovial sarcoma where median OS after 1 or 2 lines of prior chemotherapy is reported at 11.7 and 7.8 months, respectively (Savina 2017). Importantly,

CMB305 therapy avoids serious toxicity with a significantly improved safety profile when compared with available systemic therapy for subjects with synovial sarcoma.

Biomarker data analyses from studies LV305-2013-001 and IMDZ-C131 showed that subjects who developed an anti-NY-ESO-1 immune response measured by either T cells or antibodies had a trend to a better OS when compared with subjects without an induction of immune response. This effect on OS was evident in subjects who had an increase in anti-NY-ESO-1 immunity from baseline and in those who developed a de novo immune response while on therapy. Thus, the induction of anti-NY-ESO-1 immune response by CMB305 therapy appears to convey a survival advantage compared with subjects without an induction of immune response.

1.1.3 Synovial Sarcoma: An Ultra-Rare Disease with a Serious Unmet Medical Need

Synovial sarcoma, a distinct STS subtype, which affects younger subjects, is an ultra-rare disease (United States [US] incidence of between 900–1000 subjects) with a high unmet medical need (Lange 2014; Thway 2014). Currently, there is no therapy approved specifically for subjects with synovial sarcoma. Instead, therapies approved for the heterogeneous group of STS are often used and are associated with clinical outcomes that vary by sarcoma subtype.

Synovial sarcoma is a distinct subtype of STS with a pathognomonic translocation t(X;18) resulting in SS18-SSX1, SS18-SSX2, and rarely SS18-SSX4 fusion transcripts with distinct clinical features and outcomes (Ladanyi 2002; Lange 2014). B cell lymphoma 6 corepressor rearrangement (BCOR) upregulation is emerging as a common downstream pathway for synovial sarcoma with either typical SS18-SSX transcript or with rare fusion variants, such as SS18L1-SSX (Kao 2017). Approximately one-third of synovial sarcomas occur in childhood, and the peak incidence is in the third decade of life, with nearly 50% of synovial sarcomas occurring in subjects younger than 30 years of age (Ferrari 2004; Lange 2014).

Metastatic disease occurs in approximately 50% of subjects at the time of diagnosis with 80% of subjects having pulmonary lesions (Spurrell 2005). Greater than 80% of synovial tumors express NY-ESO-1, which is associated with a worse prognosis (Nicholaou 2006; Jungbluth 2001a; Van Tine 2016; Gnjatic 2006; Komarov 2017). Though subjects with synovial sarcoma are often younger, have better performance status, and relative chemosensitive disease, survival outcomes remain limited in subjects with non-curative, locally-advanced unresectable disease, and metastatic disease. There is a paucity of published literature on expected outcomes for subjects with synovial sarcoma, and no prospective randomized trial has demonstrated benefit in this population.

For subjects with non-curative locally-advanced disease or metastatic disease, chemotherapy is a palliative treatment in the vast majority of cases. In this setting, toxicity should not outweigh the potential benefits resulting from chemotherapy (Sleijefer 2005). National Comprehensive Cancer Network (NCCN) guidelines version 2.2017 and European Society for Medical Oncology (ESMO) Clinical Recommendations 2008 for STS recommend palliative chemotherapy as the primary treatment for unresectable disease or disseminated metastases. NCCN guidelines include

single agents (e.g., dacarbazine, doxorubicin, epirubicin, or ifosfamide) or anthracycline-based combination regimens (doxorubicin or epirubicin with ifosfamide and/or dacarbazine) for subjects with unresectable locally-advanced or metastatic disease. NCCN guidelines for subjects with tumors that become resectable upon completion of first-line chemotherapy (amenable to local regional therapy) are intentionally non-specific (NCCN). The survival of subjects with STS and metastatic disease is comparable to those who develop delayed metastatic disease. There is no improved survival observed for subjects with metastectomy (Kane 2002).

A phase 3 study of doxorubicin alone versus the combination of intensified doxorubicin plus ifosfamide in advanced or metastatic STS showed no difference in the primary endpoint of OS, 14.3 months versus 12.8 months (hazard ratio [HR] = 0.83 with a 95% confidence interval [CI] = 0.67–1.03) but a significantly higher secondary endpoint of median progression-free survival (PFS) with the combination regimen, 7.4 months versus 4.6 months (HR = 0.74 with a 95% CI = 0.60–0.90). The overall response was 26% (2% complete response [CR], 25% partial response [PR]) for the combination therapy and 14% (1% CR, 13% PR) for single-agent doxorubicin. Fifty percent of subjects completed 6 cycles on the doxorubicin-alone arm versus 51% of subjects on the combination arm (Judson 2014). A recent phase 2 study of doxorubicin plus olaratumab versus single-agent doxorubicin demonstrated a median PFS of 6.6 months and median OS of 26.5 months for subjects with STS. The median number of infusions was 7 in the doxorubicin plus olaratumab arm versus 4 infusions in the doxorubicin single-agent arm (Tap 2016). The NCCN guidelines recommend combination therapy with doxorubicin and olaratumab for use in STS histologies for which an anthracycline-containing regimen is appropriate. The combination of olaratumab and doxorubicin now replaces doxorubicin alone as a first-line treatment option (Helwick 2017).

Ifosfamide is an active regimen with acceptable toxicity (van Oosterom 2002) and has demonstrated significant activity in treating advanced sarcomas with a response rate (RR) of approximately 30% when used as a single agent (Rosen 1994). Standard-dose ifosfamide is active in the first-line treatment of subjects with advanced STS (overall response rates [ORRs] of 10%–25%) (Riedel 2012). In a single-center retrospective analysis, the median number of cycles of high-dose ifosfamide was 4 (Rahal 2012), and in a phase 3 trial of ifosfamide administered in 2 schedules, 20% of subjects receiving a dose of 3 g/m^2 and 30.8% receiving a dose of 9 g/m^2 completed 6 cycles (Lorigan 2007). Ifosfamide is the only drug that consistently shows RRs similar to doxorubicin without the cardiotoxicity. Synovial sarcoma in particular is thought to be highly sensitive to ifosfamide (Tascilar 2007).

A limited number of retrospective reviews have evaluated first-line practice patterns in synovial sarcoma. In a post-hoc analysis of a prospectively gathered database of subjects with synovial sarcoma, the frequency of different first-line chemotherapy regimens showed that 33% received combination ifosfamide/doxorubicin (RR 58.6%), 27% received single-agent ifosfamide (RR 25%), and 18% received single-agent doxorubicin (RR 25%) (Spurrell 2005). In a review of 15 European Organization for Research and Treatment of Cancer prospective first-line synovial sarcoma trials, 35.8% of subjects received combination ifosfamide/doxorubicin (ORR 32.2%)

and 13.4% of subjects received single-agent ifosfamide (ORR 33.3%). Even though not statistically significant, ifosfamide seemed to be the most active drug when compared with anthracycline alone (Vlenterie 2016). In a single-institution retrospective review of subjects with synovial sarcoma treated with high-dose ifosfamide, the ORR was 44% and median PFS was 11.6 months (Rahal 2012).

A recent observational study on patterns of care and outcomes in synovial sarcoma found that of 188 subjects treated, 37% did not receive an anthracycline in the first line and 61% did not receive polychemotherapy. The authors concluded that a combination of doxorubicin with a second drug, such as ifosfamide, should be used only after careful discussion with the subject on the benefit/risk ratio of this approach, particularly when tumor shrinkage is expected to improve the symptoms or clinical benefits (Savina 2017). This study also reported 49% of subjects received some form of local regional therapy of metastatic disease. One of the factors associated with a higher probability of 5-year survival was locoregional treatment of metastases (OR = 7.41; 95% CI, 4.42–12.41). However, no guidelines exist on how to best integrate local regional therapy (Savina 2017).

Preliminary IMDZ clinical data demonstrate that CMB305 may provide an advantage over or complement available approved therapies for subjects with synovial sarcoma. CMB305 therapy leads to extended tumor growth arrest in NY-ESO-1+ subjects who have evidence of progression prior to start of treatment. Long-term follow-up of phase 1 subjects indicate that CMB305 therapy may lead to a substantial improvement in OS in subjects with NY-ESO-1+ synovial sarcoma who received multiple prior therapies when compared with the published survival data (Savina 2017). Importantly, CMB305 therapy avoids serious toxicity with a significantly improved safety profile when compared with available systemic therapy for treatment of subjects with synovial sarcoma.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to:

- Evaluate the efficacy of CMB305 versus placebo using:
  - PFS, by investigator assessment, using RECIST v1.1
  - OS

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the efficacy of CMB305 versus placebo using:
  - Time- to-next treatment (TTNT)
  - Distant metastasis-free survival (DMFS)
  - Objective response rate (ORR) (defined by RECIST v1.1)

- Evaluate the safety and tolerability of CMB305 versus placebo
- Evaluate subject quality of life (QoL)

2.3 Exploratory Objective

- Evaluate the anti-NY-ESO-1 immune response and histologic and molecular changes in peripheral blood and tumor tissue and their association with clinical outcomes

3.0 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a global, randomized, double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of the CMB305 vaccine regimen versus placebo in subjects with synovial sarcoma expressing NY-ESO-1.

To be eligible, subjects must be receiving a first-line systemic anti-cancer therapy for unresectable locally-advanced or metastatic synovial sarcoma and have no evidence of progression at the time of randomization.

The study will consist of 5 periods: Pre-screening, Screening, Treatment, Post-treatment, and Long-term Follow-up.

The schedule of events for the Pre-screening and Screening periods is presented in Table 1 and the schedule of events for the Treatment through the Long-term Follow-up periods is presented in Table 2. Study flow diagrams for subjects who received a course of 4 cycles, 6 cycles, or 8 cycles of first-line systemic anti-cancer therapy are presented in Appendix 5, Figure 4, Figure 5, or Figure 6, respectively. A study flow diagram for subjects who have had a local regional therapy after first-line systemic anti-cancer therapy is presented in Appendix 5, Figure 7.

3.1.1 Pre-screening Period

The Pre-screening period is up to 151 days (Day -180 to Day -29) and commences at the time the subject and/or their legally authorized representative sign the Pre-screening informed consent form (ICF)/assent form. The Pre-screening period ends at the time the Main Study ICF/assent form is signed.

Before any Pre-screening procedures are performed, subjects (aged ≥18 years) and legally authorized representatives of subjects <18 years will provide written consent on the Pre-screening ICF and subjects aged 12 to <18 years will provide written assent. At the time of Pre-screening, subjects must still be receiving treatment with first-line systemic anti-cancer therapy. The following will be evaluated during the Pre-screening visit:

- Radiographic disease response assessment obtained at the standard-of-care time point by the investigator using RECIST v1.1

- Immunohistochemistry (IHC) test for the presence of NY-ESO-1 in an archival tumor tissue or fresh tumor tissue biopsy (tumor tissue may be from an archived sample obtained within 18 months before signing the Pre-screening ICF/assent form)

Once the investigator confirms 1) the subject has no evidence of progression (using RECIST v1.1) and 2) the IHC test results for NY-ESO-1 are positive (≥1% expression), then the subject and/or their legally authorized representative will sign the Main Study ICF/assent form.

3.1.2 Screening Period

The duration of the Screening period is 28 days (Day -28 to Day -1) and begins on the date the subject and/or their legally authorized representative sign the Main Study ICF/assent form and ends at time of randomization.

After satisfying the Pre-screening criteria, subjects (aged ≥18 years) and legally authorized representatives of subjects <18 years will provide written consent on the Main Study ICF and subjects aged 12 to <18 years will provide written assent for study participation. Once the appropriate Main Study ICF/assent form is signed, subjects will undergo additional eligibility assessments and the investigator will confirm there is no evidence of progression (using RECIST v1.1). The disease status will be assessed by the investigator (using RECIST v1.1) through a comparison of the most recent baseline images obtained during Screening to both 1) the images obtained prior to initiation of first-line systemic anti-cancer therapy and 2) the images obtained per standard-of-care during first-line systemic anti-cancer therapy to confirm there is no evidence of progression prior to randomization. Investigator assessment of radiographic images confirming best response (stable disease [SD] or better) to first-line systemic anti-cancer therapy using RECIST v1.1 will be entered into an electronic case report form (eCRF). Subjects who have a tumor response of SD with evidence of ≥15% to 20% increase in tumor burden will be submitted for Central Review to adjudicate the investigator's assessment of tumor response prior to randomization. Radiographic images from both Screening and Pre-screening will also be submitted to an independent review committee (IRC) for storage. The stored images will be available for evaluation by a central reader, if requested by the sponsor. After completion of Screening assessments and confirmation that the subject has met all eligibility requirements, the subject will be randomly assigned to one of the treatment arms using central randomization system on Day 1.

3.1.3 Treatment Period

The Treatment period will begin on the day of randomization (Day 1), which is to be within 28 days after the last dose of first-line systemic anti-cancer therapy or last day of local regional therapy, if applicable, and will continue until investigator-determined progressive disease (PD) (using RECIST v1.1), unacceptable toxicity, or 1 year after the first dose, whichever occurs first.

Subjects who meet eligibility criteria will be randomly assigned in a 1:1 ratio to receive one of the following centrally randomized treatments:

- Arm A: Placebo
- Arm B: CMB305

An interactive response technology (IRT) system will use the following stratification factors at the time of randomization:

- Disease status at screening: locally advanced unresectable (LAUR) vs metastatic
- Tumor response during screening: stable disease (SD)/partial response (PR) vs complete response (CR)/no evidence of disease (NED)
- Baseline presence of anti-NY-ESO-1 antibody (yes vs no)

Subjects who are randomly allocated to the placebo arm will not be permitted to cross-over to the CMB305-containing treatment arm at any time before study closure.

Tumor imaging assessments will be performed every 8 weeks after Day 1 and radiographic evidence of disease progression will be determined by the investigator using RECIST v1.1. Subjects with a global deterioration of health status requiring discontinuation of study treatment but without objective evidence of disease progression (symptomatic deterioration) will be considered as having PD for the purpose of determining PFS. Radiographic images (e.g., computed tomography [CT] scan or magnetic resonance imaging [MRI]) will also be submitted to an IRC for storage and will be available for evaluation by a central reader, if requested by the sponsor. Details for the collection and evaluation of radiographic images are included in the Radiology Manual provided to the study sites.

Tumor biopsy samples for NY-ESO-1 expression will be obtained from all subjects during the Pre-screening period as described in Section 3.1.1 (either archival tumor tissue or a fresh biopsy sample). All subjects will provide peripheral blood samples for anti-NY-ESO-1 antibody assay at the screening visit for stratification.

Quality of life will be assessed up to 12 months from Day 1.

Safety will be monitored by evaluating the frequency and severity of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, immunogenicity and persistence of LV305. Local laboratory test values will be used for treatment decisions and subject care; central laboratory test values will be used in the analysis of safety.

In addition, at only select US sites, the following will be collected:

Peripheral blood samples for the anti-NY-ESO-1 T cell and antibody assays will be obtained prior to start of study treatment from subjects on Day 1, Day 92, and Day 365 for subjects who have not had a progression event. A tumor biopsy will be obtained at screening, Day 92, and Day 365 for subjects who have not had a progression event. An additional tumor biopsy at time of progression event will be encouraged.

3.1.4 Post-treatment Period (For Subjects Who Discontinue Study Treatment for Reasons Other Than Disease Progression)

The Post-treatment period will begin at the end of treatment and will continue until investigator-determined radiographic PD (using RECIST v1.1) is documented.

Subjects will continue to undergo imaging until the time of disease progression. At the time of disease progression, subjects will enter the Long-term Follow-up period.

3.1.5 Long-term Follow-up Period

The Long-term Follow-up period will begin at the time investigator-determined PD (using RECIST v1.1) is documented and will continue for up to 5 years, until the date of death, or until sponsor notification of study closure.

Table 1 Schedule of Events for the Pre-Screening and Screening Periods

	Pre-Screening Period[a]	Screening Period[b]
Visit	**1**	**2**
Timeline – Day(s)	**Day-180 to Day-29**	**Day -28 to Day -1**
Procedures		
Informed consent/assent[c]	X	X
Obtain or collect tumor sample for IHC testing of NY-ESO-1 expression[d]	X	
Collect fresh tumor sample to assess tumor biomarkers (frozen and FFPE) at select U.S. sites		X
Investigator review of tumor response to first-line systemic anti-cancer therapy using RECIST v1.1[e]	X	
Obtain images collected at the standard-of-care time point for the first evaluation of response to first-line systemic anti-cancer therapy[f]	X	
Tumor imaging (CT/MRI) for baseline tumor response assessment[g]		X
Inclusion and exclusion criteria		X
Demographics and medical history		X
Tumor-specific therapy history		X
Record prior and concomitant medications		X
Blood for chemistry laboratory tests[h]		X
Blood for hematology laboratory tests[h]		X
Blood for coagulation tests laboratory tests[h]		X
HIV, hepatitis B (HepB), and hepatitis C (HepC) tests[h]		X
Blood for anti-NY-ESO-1 plasma ELISA[i]		X
Blood for circulating tumor genomics[j]		X
Urinalysis[h]		X
Pregnancy test[k]		X
Vital sign measurements[l]		X
Physical examination[m]		X
12-lead electrocardiogram		X
ECOG		X
QoL assessment		X
Blood for LV305 persistence		X

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; ELISA = Enzyme-linked immunosorbent assay; HIV = human immunodeficiency virus; ICF = informed consent form; IHC = immunohistochemistry; MRI = magnetic resonance imaging; NY-ESO-1 = New York esophageal squamous cell carcinoma-1; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors

[a] The Pre-screening period is up to 151 days (Day -180 to Day -29) and is the time from the subject and/or their legally authorized representative signing the Pre-screening ICF/assent form to the time of signing the Main study ICF/assent form. The Pre-Screening can commence at any time after first dose of first-line systemic anti-cancer therapy.

[b] The duration of the Screening period is 28 days (Day -28 to Day -1) and begins on the date the subject and/or their legally authorized representative sign the Main study ICF/assent form. At Day 1, subjects must have documented completion of first-line systemic anti-cancer therapy and must have received at least 4 to 8 cycles of therapy (or no more than 180 days of systemic anti-cancer therapy).

[c] Two informed consents (subjects aged ≥18 years and legally authorized representatives of subjects aged 12 to <18 years) or assents (subjects aged 12 to <18 years) will be used in this study. The Pre-screening ICF/assent form will allow for IHC testing of the tumor sample (fresh or archival) for the presence of NY-ESO-1 and review of the tumor images (CT or MRI) collected before administration of the first dose of first-line systemic anti-cancer therapy and at the subsequent standard-of-care time point for the first evaluation of response to first-line systemic anti-cancer therapy. The Main study ICF/assent must be signed before any Screening study-related procedures are initiated. Before the Main study ICF/assent can be signed, results of IHC testing for the presence of NY-ESO-1 (≥1% expression) must be available from the central laboratory, and the investigator-evaluated tumor response (using RECIST v1.1) to first-line systemic anti-cancer therapy must be documented.

[d] At Pre-screening, a tumor sample (fresh or archival) will be collected or obtained for the IHC testing by the central laboratory for the presence of NY-ESO-1 expression (≥1% expression). Archival tumor tissue or fresh tumor tissue will be obtained from a biopsy or a resected tumor lesion, as appropriate (tumor tissue may be from a sample obtained within 18 months before signing the Pre-screening ICF/assent form).

[e] Obtain images (CT or MRI) collected before administration of the first dose of first-line systemic anti-cancer therapy. Images will be assessed by the investigator using RECIST v1.1. Investigator assessment of all target and non-target lesions and tumor response assessment will be captured in the eCRF. Subjects who have a tumor response of stable disease with evidence of ≥15% to 20% increase in tumor burden will be submitted for central review to adjudicate the investigator's assessment of tumor response prior to randomization.

[f] Obtain and review images (CT or MRI) collected at the standard-of-care time point for the first evaluation of response to first-line systemic anti-cancer therapy. The subject's response to first-line systemic anti-cancer therapy will be assessed by the investigator using RECIST v1.1 and documented in the eCRF.

[g] Tumor imaging (CT or MRI) will be performed after completion of the planned 4-cycles to 8-cycles of first-line systemic anti-cancer therapy for the evaluation of response at baseline, as assessed by the investigator using RECIST v1.1. The images collected at this time point will serve as the baseline assessment for the efficacy evaluations. These images must be collected within 28 days after the date of last dose of first-line systemic anti-cancer therapy.

[h] Results from the central laboratory will be used to determine eligibility and for the safety analysis. Laboratory tests performed by the central laboratory will include: chemistry with liver function tests, lactate dehydrogenase, alkaline phosphatase, albumin, hematology with complete blood count with differential, HIV, HepB, and HepC. Coagulation samples will be drawn only at Screening and shipped to the central laboratory (prothrombin time, partial thromboplastin time, and international normalized ratio) for analysis. Urinalysis will be conducted at the central laboratory. All laboratory assessments to be performed are listed in Table 4.

[i] The peripheral blood on all subjects must be collected Day -28 to Day -7 during Screening and will be used for plasma ELISA testing; results of the assessment will be used for stratification and randomization.

[j] For circulating tumor genomics, please see lab manual.

[k] For FCBP, serum pregnancy testing will be performed during Screening.

[l] Vital sign measurements will include body temperature, heart rate, respiratory rate, and resting systolic and diastolic blood pressure.

[m] At Screening, the physical examination should include an evaluation of organ systems, including, but not limited to, head and neck; chest and lungs; cardiac; gastrointestinal; neurologic; endocrine; and musculoskeletal and integument. Other organ systems should be evaluated as directed by medical history or current symptoms. Measurements of body weight and height will be obtained.

Table 2 Schedule of Events for the Treatment Period through Long-term Follow-up Period

	Treatment Period								Post-Treatment Period[c]	Long-term Follow-up Period[d]
	Prime Phase							Boost Phase	Follow-up	Follow-up
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**		
Timeline – Week(s)	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**Every 8 weeks[b]**	**Every 3 months until documentation of disease progression**	**Every 3 months for up to 5 years or until date of death**
Timeline – Day(s)	**1[a]**	**22**	**36**	**50**	**64**	**78**	**92**	**Up to 1 year**		
Allowed Visit Window - Days	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±14**
Procedures										
Enrollment, stratification, and treatment allocation[e]	X									
Record prior and concomitant medications	X	X	X	X	X	X	X	X	X	X
Blood for central laboratory chemistry laboratory tests[f]	X	X		X	X		X			
Blood for central laboratory hematology[f]	X	X		X	X		X			
Urinalysis[f]	X						X			
Blood for anti-NY-ESO-1 plasma ELISA[g]	X						X			
Blood for immunity assessments[g]	X						X	X		
Blood for circulating tumor genomics[h]	X						X			
Pregnancy test[i]	X						X			
Vital sign measurements[j]	X	X	X	X	X	X	X	X		
Physical examination[k]	X	X	X	X	X	X	X	X		
12-lead electrocardiogram							X			
Tumor imaging with response assessment by RECIST v1.1 (CT scan or MRI)[l]					X			X	X	
ECOG Performance Status	X	X	X	X	X	X	X			
QoL assessment[m]	X						X	X		
Report AEs and SAEs[n]	X	X	X	X	X	X	X	X	X	X

	Treatment Period								Post-Treatment Period[c]	Long-term Follow-up Period[d]
	Prime Phase							Boost Phase	Follow-up	Follow-up
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**		
Timeline – Week(s)	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**Every 8 weeks[b]**	**Every 3 months until documentation of disease progression**	**Every 3 months for up to 5 years or until date of death**
Timeline – Day(s)	**1[a]**	**22**	**36**	**50**	**64**	**78**	**92**	**Up to 1 year**		
Allowed Visit Window - Days	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±14**
Study drug administration: Placebo (Arm A) LV305 (Arm B)	X	X		X		X				
Study drug administration: Placebo (Arm A) G305 (Arm B)			X		X		X	X[o]		
Blood for LV305 persistence[p]							X	X	X	X
Tumor biopsy[q]							X			
Survival status[r]									X	X

AE = adverse event; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; MRI = magnetic resonance imaging; NY-ESO-1 = New York esophageal squamous cell carcinoma-1; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event

[a] Day 1 will occur within 28 days after the last dose of first-line systemic anti-cancer therapy or the last day of local regional therapy. Day 1 procedures must occur within 72 hours of randomization.

[b] In the Boost Phase, tumor imaging will be performed every 8 weeks for 1 year or until investigator-determined progressive disease, using RECIST v1.1, is documented.

[c] The Post-treatment period will begin at the end of treatment and will continue until investigator-determined progressive disease, using RECIST v1.1, is documented. If a subject has reached 12 months on study without disease progression, tumor imaging will be performed every 12 weeks ±7 days until disease progression.

[d] The Long-term Follow-up period will begin at the time investigator-determined progressive disease (using RECIST v1.1) is documented and will continue for up to 5 years, until the date of death, or until sponsor notification of study closure.

[e] The following information must be available at Day 1: subjects must have documented completion of first-line systemic anti-cancer therapy and must have received at least 4 to 8 cycles of therapy (or no more than 180 days of systemic anti-cancer therapy); results of IHC testing for the presence of NY-ESO-1 (≥1% expression) must be available from the central laboratory; and the investigator-evaluated tumor response, using RECIST v1.1, to first-line systemic anti-cancer therapy must be documented.

[f] During the study dosing period, all laboratory assessments are to be performed prior to dosing. Hematology and clinical chemistry samples will be shipped to the central laboratory for safety analyses, and will include: chemistry with liver function tests, lactate dehydrogenase, alkaline phosphatase, albumin, thyroid function, and hematology with complete blood count with differential. Urinalysis will be conducted at the central laboratories. All laboratory tests to be performed are listed in Table 4.

[g] Blood for anti-NY-ESO-1 T cell assessments to be collected only for subjects on prior to dosing on Day 1 and Day 92 only at select US sites. Additional blood samples for immunity assessments will be drawn for any subject who has no evidence of tumor progression by RECIST v1.1 at 1 year at the same select US sites.

[h] For circulating tumor genomics, please see lab manual.

[i] For FCBP, serum and confirmation urine pregnancy testing will be performed by the local laboratory prior to dosing on Day 1; results must be negative. Serum pregnancy testing will be performed by the local laboratory prior to dosing on Day 92; results must be negative. Pregnancy testing will be performed more frequently as required per local regulatory authority.

[j] Vital sign measurements will include body temperature, heart rate, respiratory rate, and resting systolic and diastolic blood pressure. On the day of each dosing, vital signs will be obtained no more than 60 minutes before dosing and 30 minutes after dosing (±10-minute window).

[k] Once the Screening physical examination has been conducted, a simple symptom-directed physical examination should be performed for all subsequent visits. Measurements of body weight will be obtained at every visit.

[l] Beginning in the Treatment period, imaging will be performed at 8-week intervals after Day 1 administration of the first dose of the study drug for up to 1 year or until the time investigator-determined progressive disease, using RECIST v1.1, is documented.

[m] QoL assessments will be conducted at the study site. In addition to the screening QoL assessment, the QoL assessment will be obtained on Day 1 prior to the first dose of study drug, at Day 92, and at 6 months and 12 months after Day 1. All subjects, regardless of their disease response status, will continue to have QoL assessments performed for 12 months after Day 1.

[n] All AEs and SAEs will be collected until 30 days after administration of the last dose of the study drug. Information on any SAEs and new malignancies that come to the attention of the site staff that are considered at least possibly related to CMB305 will be collected until the time of last subject contact.

[o] After Day 92, G305 or placebo will be given on Day 148 and at 8-week intervals as a boost for up to 1 year, or until unacceptable toxicity, or investigator-determined progressive disease, using RECIST v1.1, is documented, whichever occurs first. AEs will be reported at the subsequent visit and until at least 30 days after the last dose.

[p] Peripheral blood will be collected at the following times after administration of the first dose of study drug on Day 1: no sooner than Day 92 (3 months) but up to 4 months; 6 months up to 9 months; and 1 year up to 15 months; and then yearly at no sooner than every 12 months but not more than 15 months up to the time of study closure. If all post-treatment assays are negative during the first year, then the yearly samples should be archived. Samples will be used for an assay to test for persistence of LV305.

[q] The Day 92 biopsy may be obtained within ±2 weeks of Day 92, Day 365, and at time of progression event will be encouraged at the same selected US sites per footnote "g".

[r] Survival status will be obtained by any means, which includes, but is not limited to, public records where allowed per local authority, telephone contact, during an in-clinic visit, chart review, or via communicating with an individual (e.g., family, friend, referring health care provider) who is knowledgeable of the subject's survival status. More frequent survival status updates may be obtained at the request of the sponsor.

3.2 Rationale for Study Design and Control Group

Synovial sarcoma is commonly grouped together with other STS subtypes, and while it constitutes a small subgroup of subjects within clinical studies, therapies for all types of STS are commonly used as the standard treatment for subjects with synovial sarcoma. Because STS comprises multiple tumor histologies (more than 50 histologic subtypes), patterns of care and respective clinical outcomes vary considerably by histologic subgroup (Van Tine 2016; Lee 2016; Reichardt 2014; Skafida 2017). No therapy has been approved specifically for treatment of subjects with synovial sarcoma.

Currently available systemic anti-cancer therapies carry significant safety risks when used as single agents or even greater risk when administered in combination regimens. These safety risks include cardiotoxicity, myelosuppression, nausea/vomiting, and fatigue. The aforementioned toxicities can cause significant subject morbidity and may require hospitalization and/or the use of supportive care measures such as high-dose steroids, antibiotics, and transfusions (Lee 2016).

Per NCCN, maintenance therapy refers to treating a subject with an anti-cancer therapy after maximal response to first-line induction therapy (NCCN). The goal of maintenance therapy should be to improve OS or subject QoL when compared with no treatment (Schilsky 2011). This should be an appropriate setting to study the efficacy of CMB305 in synovial sarcoma subjects. Though all subjects with advanced synovial sarcoma will inevitably progress, PFS following the initial response to first-line systemic anti-cancer therapy ranges from 6 to 8 months with up to two-thirds of subjects experiencing SD or a response (Judson 2014). Once maximum benefit has been achieved by therapy, treatment is often stopped, and subjects receive no therapy until subsequent progressive disease. Some of the subjects who were deemed unresectable prior to the first-line systemic anti-cancer therapy may undergo local regional therapy upon its completion. After such local regional control procedure, subjects will receive no therapy until progression.

CMB305 has a well-tolerated safety profile compared with other active systemic anti-cancer therapies and should not increase cumulative toxicities due to systemic anti-cancer therapy when administered in the proposed maintenance setting, which makes CMB305 an attractive option for subjects. Further, use of CMB305 is well-tolerated and therefore not anticipated to impact the ability to administer subsequent lines of alternative therapies in subjects after disease progression.

This phase 3 trial design in the maintenance setting, where no other options for treatment of synovial sarcoma are approved, will use a placebo in an effort to minimize bias. There are circumstances that justify the use of placebo, one of which is when there is no approved standard therapy (La Vaque 2001). Placebo controls are justified for “first-generation” drugs designed to fill a gap in the therapeutic armamentarium (Orentlicher 2001). The use of a placebo in a double-blind, randomized, controlled trial is the most rigorous test of treatment efficacy for evaluating a medical therapy (Castro 2007). Because there is no standard or approved therapy for subjects with synovial sarcoma who have no evidence of progression on first-line systemic

anti-cancer therapy, the use of a placebo in this trial is warranted. This trial will evaluate whether CMB305 active therapy is better than observation alone (i.e., placebo).

Advantages for the use of placebo in the control arm of this trial include:

- Lowers the risk of altering the natural history of a subject's tumor progression so that there is a true comparator arm
- Minimizes confounding factors and bias
- Reduces the potential of study withdrawal

The study will be stratified by response to first-line treatment to maintain balance between arms. The strata will allow for statistical impact of subjects who have received local regional therapy. In addition, subjects on the study are not forgoing any standard therapy, which minimizes risks and allows for blinded analysis of not only efficacy but also of QoL and the safety of CMB305.

In summary, there remains a high unmet medical need for subjects with locally-advanced unresectable or metastatic synovial sarcoma who have no evidence of progression. Currently, there is no disease-specific therapy approved specifically for the indication of synovial sarcoma based on the underlying biology or subtype specific activity. Therapeutic options that are approved for the broader STS indication have limited efficacy in subjects with synovial sarcoma and are often associated with significant toxicities. Thus, there is a need for a novel approach on how to develop and evaluate a new targeted therapy that is safe for this ultra-rare subject population with a high unmet medical need.

3.3 Study Duration and Dates

Subject participation is inclusive of the Pre-screening, Screening, Treatment, Post-treatment, and Long-term Follow-up periods.

The Pre-screening period is up to 151 days (Day -180 to Day -29) and begins from the time the subject and/or their legally authorized representative sign the Pre-screening ICF/assent form to the time the Main Study ICF/assent form is signed. The Pre-screening period can start as early as the first dose of first-line systemic anti-cancer therapy.

The duration of the Screening period is 28 days (Day -28 to Day -1) and begins on the date the subject and/or their legally authorized representative sign the Main Study ICF/assent form and ends at time of randomization. The screening window may be extended up to 56 days by the sponsor, if a patient is recovering from toxicity related to first line systemic anti-cancer therapy, or completing local regional therapy, or baseline imaging needs adjudication to determine eligibility.

The Treatment period will begin on the day of randomization (Day 1), which is to be within 28 days after the last dose of first-line systemic anti-cancer therapy or the last day of local regional therapy, if applicable, and will continue until investigator-determined radiographic PD

(using RECIST v1.1) is documented, the occurrence of unacceptable toxicity, or until 1 year after the first dose, whichever occurs first. All visits during the Treatment period will have a window of ±3 days from the day specified.

The Post-treatment period (for subjects who discontinue study treatment for reasons other than disease progression) will begin at the end of treatment and will continue until investigator-determined PD (using RECIST v1.1) is documented. All visits during the Post-treatment period will have a window of ±7 days from the day specified.

The Long-term Follow-up period will begin at the time investigator-determined PD (using RECIST v1.1) is documented and will continue for up to 5 years, until the date of death, or until sponsor notification of study closure. All visits during the Long-term Follow-up period will have a window of ±14 days from the day specified.

4.0 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 248 subjects who have synovial sarcoma expressing NY-ESO-1 will be enrolled and randomly allocated in a 1:1 ratio to treatment with CMB305 or placebo.

4.2 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study.

1. Have documented histologic diagnosis of synovial sarcoma (may be confirmed by the presence of t(X;18) (p11:q11) translocation or B cell lymphoma 6 corepressor [BCOR] rearrangement) and have disease that is unresectable locally-advanced or metastatic prior to the start of first-line systemic anti-cancer therapy. Unresectable is defined as having evidence of positive surgical margins after resection of primary disease or a documented surgical consultation with assessment of an inability of resection to provide clear margins.
2. Have IHC test results from tumor biopsy for NY-ESO-1 that are positive (≥1% expression).
3. At the time of Pre-screening, subjects must be receiving a first-line anthracycline or ifosfamide-containing systemic anti-cancer therapy regimen (single agent ifosfamide, single agent anthracycline, combination anthracycline plus ifosfamide, or combination anthracycline plus olaratumab). Subjects must have received at least 4 cycles but no more than 8 cycles of therapy (or no more than 180 days of systemic anti-cancer therapy). Subjects who have received local regional therapy (surgical resection, radiotherapy, radiofrequency ablation, or cryotherapy) are eligible if they meet the following:
    a. Subjects whose disease converted to operable after completion of first-line chemotherapy are eligible, if local regional therapy (surgical resection, radiotherapy, radiofrequency ablation or cryotherapy) is completed within the

180-day period from the date of the first dose of first-line systemic anti-cancer therapy. Please note that an extension of this 180-day period may be allowed per Section 3.3 of the protocol.

b. Subjects whose disease remains inoperable after completion of radiotherapy are eligible if radiotherapy is completed within the 180-day period from the date of the first dose of first-line systemic anti-cancer therapy and there is no evidence of progressive disease prior to initiation of radiotherapy. Please note that an extension of this 180-day period may be allowed per Section 3.3 of the protocol.

c. Subjects who have PD ≤6 months after date of last dose of adjuvant/neoadjuvant systemic anti-cancer therapy or date of last day of local regional therapy are not eligible.

4. Must have documentation of no evidence of disease progression of the tumor during or after completion of first line systemic anti-cancer therapy as determined by the investigator using RECIST v1.1 guidelines. Subjects who have a tumor response of SD with evidence of ≥15% to 20% increase in tumor burden will be submitted for Central Review to adjudicate the investigator's assessment of tumor response prior to randomization. Subjects with NED are eligible.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Age ≥12 years.
7. Have a life expectancy of at least 6 months, as determined by the investigator.
8. If a female of child-bearing potential (FCBP), willing to undergo pregnancy testing and agree to use at least 1 highly-effective contraceptive method, such methods include combined estrogen and progesterone-containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) or progesterone only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner or true sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject, refraining from heterosexual intercourse during the entire period of risk associated with study treatments) during the dosing period and for 1 month (which is the duration of a menstruation cycle) after administration of the last dose of CMB305. More stringent contraception criteria should be followed if requested by local regulatory authorities.
9. If male and sexually active with a FCBP, must be surgically sterile (i.e., vasectomy) or agree to use highly-effective contraception, such as latex condom, during the dosing period and for 3 months (which is the duration of a sperm cycle) after administration of the last dose of CMB305. More stringent contraception criteria should be followed if requested by local regulatory authorities.
10. Have recovered from the toxic effects (except alopecia) to grade 2 or better from systemic anti-cancer therapy according the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 (or newer).

4.3 Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for the study.

1. Have received the last dose of first-line systemic anti-cancer therapy or date of most recent local regional therapy >28 days prior to Day 1 (unless otherwise indicated in Section 3.3).
2. Have received prior NY-ESO-1 therapy.
3. Have received first-line systemic anti-cancer therapy with an agent other than an anthracycline-containing or ifosfamide-containing regimen (single agent anthracycline, single agent ifosfamide, combination anthracycline plus ifosfamide, or combination anthracycline plus olaratumab), or ifosfamide.
4. Have received treatment with systemic immunomodulatory agents (including, but not limited to, interleukin-2) within 28 days prior to administration of the first dose of CMB305 (i.e., Day 1) or 5 half-lives of the drug, whichever occurs sooner.
5. Have significant immunosuppression from:
    a. Concurrent, recent (≤21 days prior to administration of the first CMB305 dose [i.e., Day 1]), or anticipated need for chronic treatment with systemic immunosuppressive dose of corticosteroids (the use of physiologic doses of corticosteroids may be approved after consultation with the sponsor). The use of topical or inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.
    b. Other immunosuppressive medications (≤21 days prior to administration of the first CMB305 dose [i.e., Day 1]) including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor (anti-TNF) agents or conditions such as common variable hypogammaglobinemia.
6. Have psychiatric, other medical illness, or any other condition that, in the opinion of the investigator, prevents compliance with the study procedures or the ability to provide valid informed consent (or assent for subjects 12 to <18 years of age).
7. Have a history of uncontrolled autoimmune disease. Uncontrolled disease is defined as one requiring chronic supra-physiologic doses of systemic steroids or other forms of immunosuppression or that requires a recently increased or newly prescribed dose within 28 days of Screening.
8. Have a significant electrocardiogram (ECG) finding or cardiovascular disease, such as New York Heart Association cardiac disease (> Class II), myocardial infarction within the previous 3 months before administration of the first dose of CMB305 (i.e., Day 1), unstable arrhythmias, or unstable angina.

9. Have inadequate organ function as evidenced by:
    a. Marrow:
        i. Absolute neutrophil count (ANC) ≤1000/mm^3
        ii. Platelets <75,000/mm^3
        iii. Hemoglobin (Hgb) <8 g/dL
        iv. Lymphocytes ≤800/mm^3.
    b. Hepatic:
        i. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0× the upper limit of normal (ULN) for subjects without liver metastases **or** ≥5× ULN for subjects with liver metastases
        ii. Total serum bilirubin >1.5× ULN (**or** direct bilirubin ≥1.5 ULN for subjects with total bilirubin levels <1.5× ULN). Subjects with Gilbert's disease may be included if their total bilirubin is <3.0 mg/dL).
    c. Renal:
        i. Creatinine clearance <0.50 x LLN.
    d. For subjects not using blood thinners:
        i. Prothrombin time (PT) >1.5× ULN or international normalized ratio (INR) >1.5× ULN
        ii. Partial thromboplastin time (PTT) >1.5× ULN
        iii. Subjects using blood thinners must be able to modify their normal dosing regimen to allow for injections of investigational product.
10. History of other cancer within 3 years (except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, localized prostate cancer treated with curative intent, ductal carcinoma in situ treated surgically with curative intent, or other cancers with a similar outcome).
11. Evidence of active tuberculosis or recent (<1 week prior to first scheduled dosing on Day 1) clinically-significant infection requiring systemic therapy. (Prophylactic antibiotics [e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease] are permitted.)

12. Evidence of active HepB, HepC, or HIV infection:
    a. Active HepB is defined as having a positive HepB surface antigen (HBsAg) test result at Screening.
    b. Subjects with past/resolved HepB infection (defined as having a negative HBsAg test and a positive antibody to HepB core antigen [anti-HBc] antibody test) are eligible. HepB viral DNA results must be negative in these subjects prior to the first scheduled dosing on Day 1.
    c. Subjects with test results positive for HepC antibody are eligible only if polymerase chain reaction (PCR) testing is negative for HepC viral RNA.
    d. Subjects who are HIV positive.
13. Have had live, attenuated vaccine administered within 28 days prior to the first scheduled dosing on Day 1 or anticipate that such a live, attenuated vaccine will be required during the study.
14. Have a history of brain metastasis.
15. Have received cancer therapies, including chemotherapy, radiation, biologic or kinase inhibitors, granulocyte colony-stimulating factor (G-CSF), or granulocyte-macrophage colony stimulating factor (GM-CSF) within 3 weeks prior to the first scheduled CMB305 dosing.
16. A FCBP who is pregnant, is planning to become pregnant, or is breast feeding; or a male who is sexually active with a FCBP who is planning to become pregnant.
17. Hypersensitivity to any ingredient of either LV305 or G305.

5.0 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 CMB305

CMB305 is a novel DC-targeting active immunotherapy regimen that consists of in vivo immunization by sequential administration of 2 complementary products: LV305 (an immune priming component) and G305 (an immune-boosting component). LV305 is a DC-targeting viral vector that encodes the full-length gene of the NY-ESO-1 cancer testes antigen. G305 consists of the recombinant full-length NY-ESO-1 protein adjuvanted with the synthetic TLR4 agonist GLA.

5.1.1.1 LV305

The LV305 product (priming component of the vaccine regimen) is a purified DC-tropic, replication-incompetent, integration-deficient, third-generation LV generated from our ZVex vector platform, which encodes the NY-ESO-1 cancer testes antigen. Like other third-generation

LVs, ZVex is devoid of all HIV 1-derived accessory proteins, except for Rev (regulator of expression of virion proteins [Lentivirus accessory protein]), and is encoded by a split genome with a deletion in the U3 region (ΔU3, for self-activation of the 3´LTR) (Dull 1998). The ΔU3 deletion is a self-inactivating mutation that: (1) prevents transcription of the full-length vector genome from reversed transcribed double-stranded DNA vectors in the infected target cell (Miyoshi 1998), and (2) minimizes the risk of insertional activation that can occur when a 3´LTR can function as a promoter after integration. In addition, the ZVex vector platform has been pseudotyped with a modified Sindbis virus envelope protein (SINVar1) (Morizono 2010) to selectively target DCs.

LV305 is formulated in Tris buffer containing 5% sucrose and 50 mM L-arginine at pH 7.5. The LV305 drug product is produced at the nominal concentration (product strength) of 1×10^{10} vector genomes (vg)/mL, 1.4 mL per vial.

5.1.1.2 G305

The G305 product (immune-boosting component of the vaccine regimen) is composed of the recombinant NY-ESO-1 protein admixed with GLA in a stable emulsion. G305 is supplied in a 2-vial configuration. One vial contains the formulated NY-ESO-1 protein and the second vial contains the adjuvant, GLA-SE.

5.1.1.2.1 NY-ESO-1

NY-ESO-1 is a protein of 182 amino acids, produced in Escherichia coli. The theoretical molecular weight of the recombinant NY-ESO-1 protein is 18,146.5 daltons. The amino acid sequence of NY-ESO-1 is:

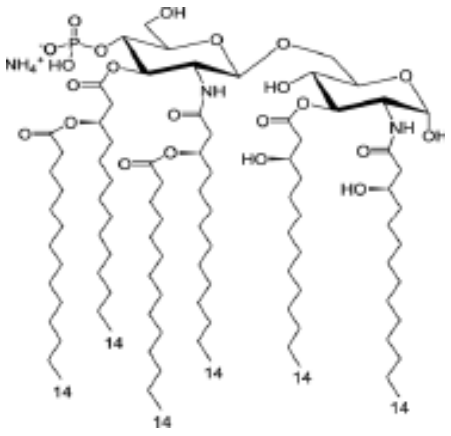
GPMQAEGRGT GGSTGDADGP GGPGIPDGPG GNAGGPGEAG ATGGRGPRGA GAARASGPGG GAPRGPHGGA ASGLNGCCRC GARGPESRLL EFYLAMPFAT PMEAELARRS LAQDAPPLPV PGVLLKEFTV SGNILTIRLT AADHRQLQLS ISSCLQQLSL LMWITQCFLP VFLAQPPSGQ RR

The NY-ESO-1 drug product consists of 0.65 mL of purified, aseptically filtered NY-ESO-1 drug substance (containing 0.5 mg/mL NY-ESO-1 protein, 50 mM glycine, 3 M urea [pH 9.0] and 0.05% polysorbate 20) in 2-mL vials.

5.1.1.2.2 GLA-SE

GLA-SE is a fully synthetic TLR4 agonist (GLA) in an SE formulation comprising squalene (oil), glycerol, α-tocopherol (vitamin E), dimyristoylphosphatidylcholine (DMPC), surfactant (poloxamer) and ammonium phosphate buffer. GLA-SE is packaged in 3-mL single-use vials. The chemical structure of GLA is provided in Figure 2.

Figure 2 GLA Structure



5.1.2 Placebo

The matching placebo for CMB305 will include matching placebos for each component of the vaccine: 1 for LV305 and 2 for G305.

5.1.2.1 LV305 Placebo

The matching placebo for LV305 will be normal saline.

5.1.2.2 G305 Placebo

5.1.2.2.1 NY-ESO-1 Placebo

The matching placebo for the NY-ESO-1 component of G305 will be normal saline.

5.1.2.2.2 GLA-SE Placebo

The matching placebo for the GLA-SE component of G305 will be the non-active SE.

5.2 Treatments Administered

LV305 will be administered on Days 1, 22, 50, and 78. For each day of administration, the LV305 daily dose of 4×10^{10} vg will be given as 4 separate 1-mL SC injections of 1×10^{10} vg/mL administered preferably to a separate extremity (upper or lower limb [or stump if subject had prior resection]). If injection to a separate extremity is not feasible, then each SC injection should be at least 3 cm from the neighboring injection site of the same extremity.

G305 is an admixture of NY-ESO-1 and GLA-SE described in the Pharmacy Manual. G305 will be administered via IM injection in the anterior upper thigh or deltoid region on Days 36, 64, and 92, and then at 8-week intervals up to 1 year or until investigator-determined PD (using RECIST v1.1) is documented or unacceptable toxicity, whichever occurs first. The quantity of

recombinant NY-ESO-1 protein is fixed at 250 µg/dose, and the dose of GLA-SE will be 5 µg of GLA in a 2% oil-in-water emulsion. The limb or stump used for injection will be alternated with each treatment.

Three placebos (fully matched to characteristics of LV305, the NY-ESO-1 protein, and GLA-SE) will be provided for this study and will be administered on the same schedule and by the same route as the corresponding experimental therapy components to ensure that the sponsor, site personnel (including pharmacist), and subjects remain blinded to study drug for the duration of the study.

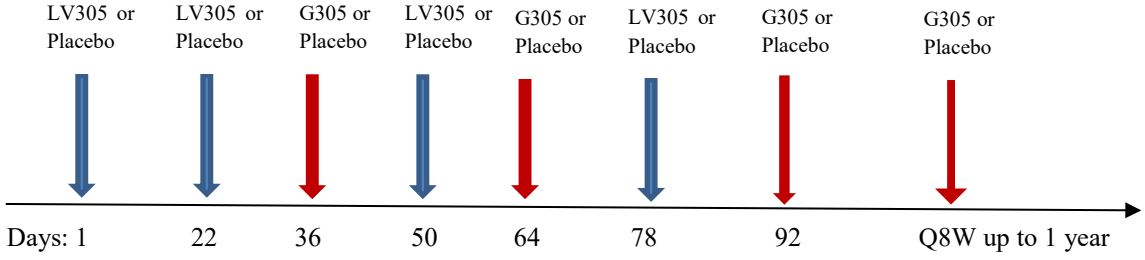
Matching placebo for LV305 will be administered by the same route and on the same days as LV305; matching placebos for G305 will be mixed per the Pharmacy Manual in the same manner as the product G305 and then administered by the same route and on the same days as G305.

Full details on the administration of CMB305 and matching placebo will be provided in the Pharmacy Manual provided to study sites.

5.3 Selection and Timing of Dose for Each Subject

The CMB305 or matching placebo dosing regimen is presented in Figure 3. The proposed CMB305 regimen for this study consists of 4×10^{10} vg of LV305 (administered SC as 4 injections of 1×10^{10} vg, with one injection preferably given to each upper arm and each upper leg at each visit) on Days 1 and 22. On Day 36 (2 weeks after Day 22) the boost, G305, will be administered. Thereafter, alternating doses of LV305 and G305 will be administered every 2 weeks until Day 92. In total, 4 doses (16 SC injections) of LV305 and 3 doses (3 IM injections) of G305 will be administered through Day 92. G305 will then be administered IM at 8-week intervals for up to 1 year or until the time investigator-determined PD (using RECIST v1.1) is documented or unacceptable toxicity occurs, whichever occurs first. Details on the preparation and administration are provided in the Pharmacy Manual.

Figure 3 CMB305 or Matching Placebo Dosing Regimen



IM = intramuscular; Q8W = every 8 weeks; SC = subcutaneous

LV305 or matching placebo is administered as 4 separate 1-mL SC, each preferably administered in a separate upper or lower limb (or stump if the subject has had a resection), or administered at least 3 cm from the neighboring injection site if on the same limb/stump. G305 or matching placebo is administered IM.

5.4 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly allocated in a 1:1 ratio to receive placebo (Arm A) or CMB305 (Arm B) according to a centrally randomized treatment schedule.

An IRT system will use the following stratification factors at the time of randomization:

- Disease status at screening: locally advanced unresectable (LAUR) vs metastatic
- Tumor response during screening: stable disease (SD)/partial response (PR) vs complete response (CR)/no evidence of disease (NED)
- Baseline presence of anti-NY-ESO-1 antibody (yes vs no)

5.5 Blinding

The study subjects, investigators, study site personnel, including the pharmacist, safety laboratory personnel, central imaging readers, sponsor, and representatives of the sponsor involved in the conduct and/or management of the study will be blinded to treatment assignment.

LV305 and its placebo will be identical in appearance; G305 and its placebos will be identical in appearance.

All study treatments (CMB305 or placebo) will be labeled with the study number, a unique number, and any additional information required in accordance with government regulations. Further details will be contained in the Pharmacy Manual provided to study sites.

The blind may be broken in case of a medical emergency when unblinding the treatment is necessary to manage the treatment of a subject. The investigator has the ability to perform unblinding immediately according to emergency unblinding procedures.

5.6 Treatment Modification and Discontinuation

There are no protocol allowed dose reductions or increases.

5.6.1 Treatment Interruptions

If less than a full dose of a study treatment component (LV305 or G305) is administered (eg, less than the four (4) injections of LV305/placebo), document the injections that were administered and the reason the other injections were not administered. The missed injections will not be administered at a later time. Treatment should resume according to the next scheduled dose and visit.

5.6.2 Treatment Delay

Administration of a study treatment component (LV305 or G305) will be delayed for the following adverse reactions:

- A drug-related non-hematological toxicity ≥Grade 2, with the exception of toxicity listed under requirement of permanent discontinuation of study treatment; Grade 2 fatigue alone does not require the withholding of study treatment;
- A drug-related hematological toxicity Grade 4.

Study treatment will resume according to schedule if drug-related toxicity improves to ≤Grade 1 within 4 weeks of onset. If Grade 2 toxicity stabilizes based on the investigator assessment (subject is asymptomatic and controlled), study treatment may resume after consultation with and approval by the Sponsor.

5.6.3 Treatment Discontinuation

Permanent discontinuation of a study treatment component (LV305 or G305) responsible for an adverse event should be considered following discussion with the Sponsor if any of the following drug related adverse events are experienced:

- Severe or life-threatening drug-related adverse events;
- Grade 2 or above drug related adverse events which persist without improvement for >4 weeks. With Investigator and Sponsor agreement, subjects with a drug-related adverse event still at Grade 2 may continue in the study only if asymptomatic and controlled.

For subjects who experience a recurrence of the same ≥Grade 3 drug-related adverse events with rechallenge of study treatment component (LV305 or G305), a consultation between the Sponsor and Investigator will occur to determine whether therapy with study treatment component responsible for the event should be discontinued. A subject who experiences the same drug-related serious adverse events (SAE) of the same Grade or higher with rechallenge, therapy with study treatment component responsible for the event must be discontinued immediately.

5.7 Concomitant Therapy

Except for excluded medications (Section 5.8), medications for symptoms and supportive management are permitted. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an AE), the treatment must be recorded on the source document and eCRF, including the reason for treatment, name of the drug, dosage, route, and date of administration. All medications including prescription, over-the-counter (OTC), herbal, and other nutritional vitamins and/or supplements taken within 60 days of Day 1 will be recorded on the eCRF.

5.8 Restrictions

In addition to the restrictions specified in Section 4.3, Exclusion Criteria; subjects must comply with the following restrictions.

5.8.1 Prior Therapy

Subjects cannot have received prior treatment with the following:

- NY-ESO-1-directed immunotherapies

Subjects must have received the last dose of first-line systemic anti-cancer therapy, or the last day of treatment with local regional therapy, if applicable, no more than 28 days prior to Day 1.

The following are prohibited within 21 days prior to the first administration of CMB305 on Day 1 or 5 half-lives of the drug (whichever is sooner):

- Any investigational agent or cancer therapy
- Immunomodulatory agents (including, but not limited to, interleukin-2)

The following are prohibited within 21 days prior to the first administration of CMB305 on Day 1:

- Immunosuppressive medications, including but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents
- Any systemic anti-cancer therapy or local regional therapy (surgical resection, radiotherapy, radiofrequency ablation, cryotherapy)

5.8.2 Prohibited Concomitant Therapy

The following treatments will be prohibited from Day 1 through the end of treatment or until investigator-determined PD (using RECIST v1.1) is documented:

- Any investigational drug other than LV305 or G305 is prohibited prior to documentation of investigator-determined PD (using RECIST v1.1).
- Any chronic treatment with systemic immunosuppressive dose of corticosteroid at supra-physiologic doses within 28 days prior to administration of the first dose on Day 1 through the end of treatment or until investigator-determined PD (using RECIST v1.1) is documented. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
- Other concurrent immunosuppressive medications such as methotrexate, cyclosporine, or azathioprine are prohibited prior to documentation of investigator-determined PD (using RECIST v1.1).
- Concomitant systemic anti-cancer therapy prior to documentation of investigator-determined PD (using RECIST v1.1) is prohibited for symptomatic deterioration or for subjects with NED at time of study entry who develop a new malignant lesion.

- Any systemic anti-cancer therapy or local regional therapy (surgical resection, radiotherapy, radiofrequency ablation, cryotherapy) prior to documentation of investigator-determined PD (using RECIST v1.1), or documented symptomatic deterioration, or for subjects with NED at time of study entry who develop a new malignant lesion.

5.9 Treatment Compliance

All doses of study drug will be administered under the supervision of the investigator or identified sub-investigator(s). Appropriate study personnel will maintain records of study drug receipt and dispensing. Any discrepancy regarding the dose administered and the reason for the discrepancy will be recorded in the eCRF.

5.10 Packaging and Labeling

CMB305 and its matching placebos will be manufactured, packaged, and labeled according to Good Manufacturing Practices (GMP) and Good Clinical Practices (GCP).

5.11 Storage and Accountability

Full details on the storage of CMB305 and matching placebo will be provided in the Pharmacy Manual and on the investigational product label.

LV305 drug product is stored at -90°C to -60°C. For G305, the NY-ESO-1 protein is stored at -90°C to -60°C and GLA-SE is stored at 2°C to 8°C.

Under no circumstances is it permitted to use study supplies for any purposes other than those specified in this protocol.

The investigator or a medically qualified, authorized delegate will be provided with forms to enable accurate recording of all study doses at the study site at all times. The investigator, or designee, must sign a statement that he/she has received study drug supplies intended for the study. At any given time, the amount of study drug supplied, used, and unused at the study site must match. An accounting must be given of any discrepancies.

6.0 STUDY PROCEDURES

All study procedures detailed in Sections 6.1 to 6.3 will be performed at the time points stipulated in the schedule of events for the Pre-Screening and Screening periods (Table 1) and for the Treatment through Long-term Follow-up periods (Table 2).

6.1 Informed Consent or Assent

All subjects and legal authorized representatives must provide written informed consent (if ≥18 years of age) or assent (if 12 to <18 years of age) at Pre-screening and Screening. Two informed consents/assents will be used.

The Pre-screening ICF/assent form will allow for IHC testing of the tumor sample (fresh or archival) for the presence of NY-ESO-1, and review of the tumor images (CT or MRI) collected before and after administration of the first dose of first-line systemic anti-cancer therapy.

The Main Study ICF/assent allows for participation in the study and must be signed before initiation of any Screening study-related procedures. Before the Main Study ICF/assent can be signed, results of IHC testing for the presence of NY-ESO-1 (≥1% expression) must be available from the central laboratory, and the investigator-evaluated tumor response (SD or better using RECIST v1.1) to first-line systemic anti-cancer therapy must be documented.

Prior to any involvement in study-related activities, an institutional review board (IRB)/independent ethics committee (IEC)-approved written ICF/assent must be signed and dated by the subject and/or by the subject's legally acceptable representative according to local regulations. Documentation of local regulations regarding what constitutes legally acceptable representation should be filed at the study site. A copy of the signed and dated ICF and any other required forms to meet local or country-specific regulations must be given to the subject and the legally acceptable representative. During the consent process, the person obtaining consent must inform the subject of all elements of the study. No protocol-specific procedures, including screening procedures, are to be performed until the subject has signed and dated an IRB/IEC-approved ICF/assent. The study begins with the signing and dating of the Main Study ICF/assent form.

6.2 Demographics and Medical History

Subject demographic data such as age, sex, ethnicity (where legally allowed), and race will be obtained during Screening.

The subject's clinically significant and relevant medical history will be obtained at Screening. The medical history should include (but not be limited to) clinically significant and relevant medical history with following body systems: head, eyes, ears, nose, and throat (HEENT), neurologic and psychiatric, endocrine and metabolic, dermatological, cardiovascular, respiratory, gastrointestinal, genitourinary, musculoskeletal, hematologic, lymphatic, hepatic and renal,

immunological, and surgical history. Medical history data will be reviewed and updated, as appropriate, at Day 1.

6.3 Efficacy Assessments

6.3.1 Tumor Imaging and Response

Subjects will have imaging performed at the time points stipulated in the schedule of events (Table 1 and Table 2).

For individual subjects, the same imaging method should be used for all subsequent image collections throughout the study. The preferred method of imaging is via CT scan with intravenous (IV) contrast (MRI may also be considered as indicated). The slice thickness of images obtained at Pre-screening (i.e., after treatment with first-line systemic anti-cancer therapy), Screening, or while on study must be the same size or smaller than the slice thickness of the image obtained prior to administration of the first dose of first-line systemic anti-cancer therapy used to document all lesions present during staging of the synovial sarcoma. All images must include windows of the chest, abdomen, and pelvis. Brain images will be obtained if symptoms or signs suggest central nervous system involvement. Bone images will be obtained if symptoms, signs, or history suggest bone involvement by metastatic disease.

All images will be evaluated by the investigator using RECIST v1.1 measurement criteria expressed as PR, CR, SD, or PD (see Appendix 1).

Radiographic images (e.g., CT scan or MRI) will also be submitted to an IRC for storage and will be available for evaluation by a central reader, if requested by the sponsor. Subjects who have a tumor response of SD with evidence of $\geq$15% to 20% increase in tumor burden will be submitted for evaluation by a central reader for adjudication.

The Radiology manual includes complete details for the collection, storage, and evaluation of images.

6.3.1.1 Imaging at Pre-screening

For subjects to be eligible for study participation, the investigator must confirm no evidence of disease progression while the subject is receiving treatment with first-line systemic anti-cancer therapy for unresectable locally-advanced or metastatic disease. During the Pre-screening period, imaging will be performed per standard-of-care and all target and non-target lesions documented before initiating first-line systemic anti-cancer therapy using RECIST v1.1. The images obtained during Pre-screening will be compared with images obtained before the start of first-line systemic anti-cancer therapy, which should have been obtained no more than 60 days prior to administration of the first dose of first-line systemic anti-cancer therapy. For a subject who has no digital images available but has a documented response classification per RECIST v1.1, a radiologist's report certifying no disease progression may be used in individual cases after prior approval by the sponsor.

6.3.1.2 Imaging at Screening

During the Screening period, and before randomization, imaging (images will include all organ systems that had disease present prior to start of first-line systemic anti-cancer therapy) will be performed, and all target and non-target lesions that were documented during Pre-screening will be assessed by the investigator using RECIST v1.1 to determine the subject's response to first-line systemic anti-cancer therapy. The images obtained at Screening will be compared with both images obtained at Pre-screening and images obtained before the start of first-line systemic anti-cancer therapy to ensure that no disease progression has occurred. Subjects who have a tumor response of SD with evidence of ≥15% to 20% increase in tumor burden will be submitted for central review to adjudicate the investigator's assessment of tumor response prior to randomization. For individual subjects, the images obtained during the Screening period must have been collected using the same imaging method used for all images. Radiographic images at Screening (e.g., CT scan or MRI) will also be submitted to an IRC for storage and will be available for evaluation by a central reader, if requested by the sponsor. Details for the collection and evaluation of radiographic images are included in the Radiology Manual.

6.3.1.3 Imaging During Treatment to the Time of Disease Progression

Tumor imaging assessments will be performed and evaluated every 8 weeks after Day 1 until investigator-determined PD (using RECIST v1.1) is documented. Disease progression will be assessed by the investigator using RECIST v1.1. For each subject, the images obtained during the Treatment period must have been collected using the same imaging method for all images during the Pre-screening and Screening periods. Subjects who have a global deterioration of health status that is attributed to progressive disease and leads to discontinuation of study treatment, but who are unable to provide radiographic evidence of disease progression (symptomatic deterioration), will be considered as having PD at the time of documented global deterioration of health for the purpose of determining PFS. Radiographic images (e.g., CT scan or MRI) will also be submitted to an IRC for storage and will be available for evaluation by a central reader, if requested by the sponsor. Details for the collection and evaluation of radiographic images are included in the Radiology Manual.

6.3.2 Immune Response Assessments

Results for anti-NY-ESO-1 plasma antibody must be available for subject stratification at the time of randomization. In addition, at select US sites, pre- and post-treatment anti-NY-ESO-1 plasma antibodies may be used for exploratory analyses.

Pre- and post-treatment blood and tumor samples will be collected for exploratory analyses of potential biomarkers of CMB305 immunogenicity and clinical tumor response as shown in Table 3.

Circulating tumor genomics will be collected for exploratory analyses of potential immune response effect on tumor growth.

Table 3 At Select US Sites Only: Immune Response Assessments

Assessment	Subjects/Timepoint	Analysis
Presence of T cell immunity at baseline (peripheral blood)	Day 1 prior to dosing	NY-ESO-1-specific T cells are detected in PBMC by ELISPOT (ex vivo or following 7-day in vitro stimulation). The assay is performed in quadruplicate. Positive response is defined as follows: • ex vivo ELISPOT: no less than 15 IFNγ-secreting spots per well after background subtraction • in vitro stimulation ELISPOT: no less than 50 spots per well after background subtraction
Presence of antibody at baseline (peripheral blood)	Screening	NY-ESO-1 specific plasma antibodies that are detected by ELISA at a titer of ≥1:100
Induction of antibody on treatment (peripheral blood)	Day 92	• NY-ESO-1 specific plasma antibodies that are detected by ELISA at a ≥4-fold increase in titer at Day 92 or • Seroconversion of NY-ESO-1 specific plasma antibodies that are detected by ELISA at 92
Induction of T cells on treatment (peripheral blood)	Day 92 and only Day 365 for subjects who have not yet progressed	• Ratio of post-treatment to pre-treatment NY-ESO-1-specific T cell counts ≥2 or • Post-treatment positive ELISPOT from pre-treatment negative baseline
Intratumoral immune status at baseline and on treatment (tumor biopsy)	Fresh biopsy either at Prescreening or Screening, Day 92, Day 365, and at time of progression event will be encouraged	Ratio of post-treatment to pre-treatment NY-ESO-1-specific T cells within the tumor

ELISA = enzyme-linked immunosorbent assay; ELISPOT = enzyme-linked immunospot;
NY-ESO-1 = New York esophageal squamous cell carcinoma-1; PBMC = peripheral blood mononuclear cells

Many exploratory analyses for potential biomarkers are being investigated, but the predictive value of such tests is not yet known. The data collected from these exploratory tests will help to define a set of biomarkers that might be used in future studies to help define the ability of CMB305 to stimulate anti-tumor immune responses and to help stratify subjects who might respond to these treatments. Exploratory blood tests may include functional assays of cytolytic T cells or other immune cells directed against autologous tumor cells or surrogate target cells,

modifications of current assays to detect anti-tumor cellular immunity, detection and/or analyses of circulating tumor cells, or analyses of other (not yet undefined) tumor markers and immune function. Screening and post-treatment cancer biopsy tissue may be collected at select study sites and only if tumor sites are accessible. These tumor samples will be examined for evidence of anti-tumor cellular immunity (e.g., CD8 T cell or natural killer cell infiltration, tumor necrosis) by IHC and for evidence of immune suppression within the tumor microenvironment. Samples may also be sent for gene expression analysis, T cell receptor expression, fluorescence-activated cell sorting analysis, and isolation of tumor-infiltrating lymphocytes. Any blood or tumor samples will only be used to examine the subject's immune response, their cancer, or to help evaluate any potential toxicity arising in the study. The samples will not be examined for unrelated research or to examine unrelated genes or diseases.

The following immune monitoring may be conducted:

- Cellular immunogenicity by changes from baseline and over the course of the trial period in peripheral blood levels of NY-ESO-1 antigen specific T cells and T cell associated cytokine production
- Cellular immunogenicity by changes from baseline and over the course of the trial period in peripheral blood levels of overall T cell effector and memory populations
- Humoral immunogenicity as measured by changes from baseline and over the course of the trial period with anti-NY-ESO-1 antibodies and anti-LV antibodies

Details for sample handling and assay performance will be provided in the Laboratory Manual provided to study sites.

6.3.3 Tumor Biopsy

Biopsy samples will be collected as specified in the schedule of events (Table 1, Table 2) and in accordance with the site's standard operating procedures. Details of biopsy collection are included in the Laboratory Manual.

6.3.4 ECOG

ECOG scores will be obtained according to the schedule of events (Table 1, Table 2). The ECOG assessment tool is provided in Appendix 2.

6.3.5 QoL Assessment

Quality of life will be assessed using a paper form completed by the subject according to the schedule of events (Table 1, Table 2) using the EuroQol 5-Dimension 5 Level (EQ-5D-5L). for subject ≥18 years of age as shown in Appendix 3. or using the EuroQol 5-Dimension Youth (EQ-5D-Y) for subjects 12 to <18 years of age as shown in Appendix 4.

6.4 Safety Assessments

The investigator is responsible for the appropriate medical care and safety of subjects who have entered this study. The investigator must notify the sponsor within 24 hours if any of the following events occurs:

- Any grade 3 or higher event, regardless of relationship to the study drug(s)
- Any event meeting the criteria for an SAE
- Any medical event of interest (MEOI) (see Section 6.4.7.5)

Safety assessments will include solicited and unsolicited symptoms, physical examination findings, vital signs, documentation of AEs, ECGs and/or echocardiogram as applicable, clinical laboratory evaluations, deviations or discontinuations attributed to AEs, concomitant medication use, and LV305 persistence.

6.4.1 Physical Examination

A physical examination will be performed at Screening and should include an evaluation of organ systems, including, but not limited to, head and neck; chest and lungs; cardiac; gastrointestinal; neurologic; endocrine; and musculoskeletal and integument. Other organ systems should be evaluated as directed by medical history or current symptoms. At subsequent visits, limited, symptom-directed physical examinations should be performed.

Measurements of weight and height will be recorded only at screening and weight at every visit.

6.4.2 Vital Signs

Vital sign measurements will include systolic/diastolic blood pressure, respiratory rate, heart rate, and body temperature. On the day of each dosing, vital signs will be obtained before dosing and 30 minutes after dosing (±10-minute window). Blood pressure and heart rate will be measured no more than 60 minutes before the scheduled dosing. Vital signs should be performed before invasive procedures (e.g., blood sample collection).

6.4.3 Clinical Laboratory Tests

6.4.3.1 Laboratory Parameters

Central laboratory parameters to be analyzed are shown in Table 4. Screening laboratory measurements will be used to determine study eligibility. Central laboratory measurements will be used for safety analyses and for other exploratory data analyses. Data on local laboratory tests may be collected for subjects experiencing adverse events upon sponsor notification. Sites will collect and analyze blood and urine samples at local laboratories based on their routine practice.

Table 4 Clinical Laboratory Tests (Central Laboratory)

Hematology	Hematocrit (Hct); hemoglobin (Hgb); mean corpuscular hemoglobin (MCH); mean corpuscular hemoglobin concentration (MCHC); mean corpuscular volume (MCV); platelet count; red blood cell (RBC) count; white blood cell (WBC) count with differential; absolute neutrophil count (ANC); absolute lymphocyte count
Serum Chemistry	Albumin; alkaline phosphatase; alanine aminotransferase (ALT); aspartate aminotransferase (AST); total protein; blood urea nitrogen (BUN); calcium; carbon dioxide; chloride; creatinine; creatinine clearance; uric acid; gamma-glutamyl transferase (GGT); glucose; lactate dehydrogenase (LDH); phosphorus; potassium; sodium; total bilirubin; direct bilirubin; thyroid stimulating hormone (TSH) (if TSH abnormal then T_3, T_4 to be evaluated)
Coagulation	Prothrombin time (PT); partial thromboplastin time (PTT); international normalized ratio (INR)
Urinalysis	Appearance; bilirubin; color; glucose; ketones; microscopic examination of sediment; nitrite; occult blood; pH; protein; specific gravity; urobilinogen
Viral tests	Hepatitis B (HepB), hepatitis C (HepC), or human immunodeficiency virus (HIV) infection

6.4.3.2 Sample Collection, Storage, and Shipping

Complete details for sample collection, storage, and shipping to the central laboratory are included in the Laboratory Manual.

6.4.4 Electrocardiogram

A standard 12-lead ECG will be obtained. Subjects should rest in the supine position before each 12-lead ECG recording is started. The ECGs should be reviewed, signed, and dated by a qualified health care practitioner and any clinically important finding recorded on the ECG report and on the appropriate eCRF. The investigator is responsible for providing the interpretation of all ECGs.

6.4.5 Concomitant Medication Use

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drug. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment or prophylaxis of an AE), the treatment must be recorded on the eCRF, including the reason for treatment, generic name of the drug, dosage, route, and date of administration. Restricted and prohibited concomitant medication use is presented in Section 5.8.

The use of concomitant medications will be recorded from Day 1 through the end of the Treatment period or until the time of disease progression. Details of concomitant medication use should include the name, dose, route of administration, and indication.

6.4.6 LV305 Persistence

Peripheral blood will be collected at Screening and at the following timepoints after administration of the first dose of study drug on Day 1: no sooner than Day 92 (3 months) up to 4 months; from 6 months up to 9 months; and from 1 year up to 15 months; and then yearly at no sooner than every 12 months but not more than 15 months until study closure. If all post-treatment assays are negative during the first year, then the yearly samples should be archived. Samples will be used for an assay to test for persistence of LV305.

6.4.7 Adverse Events Assessments

All subjects who receive at least 1 study injection or another study-related procedure will be considered evaluable for safety. This includes any untoward signs (including abnormal laboratory findings) or symptoms experienced by the subject from the time of enrollment until 30 days post administration of the last dose of the study drug (i.e., CMB305). Safety will be evaluated for all treated subjects using the NCI-CTCAE v.4.03 or newer. Safety assessments will be based on medical review of both solicited and spontaneously reported AEs, including symptoms, physical examination findings, vital signs, laboratory findings, ECGs, and treatment discontinuations due to AEs. The nature, severity, and frequency of AEs will be monitored on an ongoing basis for risk assessment and to determine if risk management interventions are warranted (e.g., expedited notification of safety findings to investigators, IRBs/IECs, or regulators; update of Investigator's Brochure and ICF risks and re-consenting study subjects; revision of safety monitoring procedures; revision of eligibility criteria or other study procedures).

6.4.7.1 Adverse Event Collection Period

All enrolled subjects will have periodic assessment of clinical and laboratory AEs. All AEs, SAEs, and MEOIs will be collected until at least 30 days after administration of the last dose of the study drug (i.e., CMB305). MEOIs, immune-mediated events and secondary malignancies (regardless of causality) to be reported through 90 days following last IP dose/cessation of treatment or 30 days after initiation of new anti-cancer therapy, whichever is earlier, need to be reported to the Sponsor within 24 hours of event in the same manner as outlined for SAEs. All SAEs and new malignancies that come to the attention of the site staff and are considered at least possibly related to CMB305 will be collected until the time of last subject contact. AEs are to be reported 30 days after last dose of study drug if possibly related to CMB305/blinded IP, unless they fall in category above.

6.4.7.2 Adverse Event Reporting

All SAEs that are unexpected and considered possibly, probably, or definitely related to study drug by the investigator or sponsor will be reported to the Food and Drug Administration (FDA), applicable regulatory agencies, and IRB/IEC in accordance with the requirements in 21 Code of Federal Regulations (CFR) §312.32 and International Conference on Harmonization (ICH) guidelines.

At each study visit (including unscheduled visits), the investigator, or designee, will determine whether any AEs have occurred. Each AE will be reported in the subject's medical record and on the AE eCRF page and classified according to the criteria in Section 6.4.7.4, Section 6.4.7.6, and Section 6.4.7.7. If known, the diagnosis should be recorded, in preference to the listing of individual signs and symptoms. Any pre-existing conditions that are detected as part of the initial screening procedures will be reported in the medical history and not as an AE. However, pre-existing conditions that worsen after enrollment should be reported as an AE.

Adverse events will be reported to the FDA and applicable regulatory authorities in accordance with the requirements outlined in 21 CFR §312.32 and ICH guidelines. Progression of cancer is not considered an AE unless it is considered to be drug-related by the investigator. Deaths due to cancer progression will not be reported as expedited events. The investigator will continue to monitor the subject until any new, changed, or worsened AE resolves, returns to baseline, or until the investigator and IMDZ agree that follow-up is no longer necessary. AEs must be followed until resolution whenever possible.

6.4.7.3 Serious Adverse Event Reporting

If an SAE occurs, IMDZ will be notified within 24 hours of awareness of the event by the investigator. In particular, if the SAE is fatal or life-threatening, IMDZ must be notified immediately, irrespective of the extent of available AE information. In the rare event that the investigator or designee does not become aware of the occurrence of an SAE immediately, the investigator or designee must report the event within 24 hours of their awareness and document the time of when his/her first awareness occurred. For all SAEs, the investigator or designee is obligated to pursue and provide information to IMDZ in accordance with the time frames for reporting specified above. In addition, an investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE case report form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of causality.

New SAEs experienced by subjects during the Screening period (pre-study treatment) will be reported to IMDZ if the events are considered related to study procedures. New SAEs determined to be related to study tests or procedures (not including cancer-related events) and any hospitalizations determined to be related to study tests or procedures that are experienced by subjects from the time of signing the Main Study ICF/assent form until Day 1 (start of CMB305

treatment) will be noted on the SAE form and eCRF. From Day 1 until 30 days after administration of the last dose of the investigational product (i.e., CMB305), any new SAE will be noted on the SAE form and eCRF. After that point, any AE that comes to the attention of the site staff that may be causally related to study drug, i.e., CMB305, (i.e., there is a reasonable possibility that the event may have been caused by the drug) will be reported to IMDZ.

SAEs will be monitored until they have resolved, returned to baseline, or they are not clinically significant, stable, or do not require additional follow-up, as judged by the investigator and IMDZ.

STUDY CONTACT FOR REPORTING SERIOUS ADVERSE EVENTS	
Vendor:	Everest Clinical Research, Corp.
Telephone:	PPD (office) or PPD (mobile)
Email:	SAE forms must be completed electronically in the EDC clinical database. Back-up SAE report forms or supplemental information is to be emailed to: PPD

6.4.7.4 Medical Event of Interest Reporting

Selected non-serious AEs, as described in Section 6.4.7.5, are classified as MEOIs and must be recorded as such on the AE CRF and reported to the sponsor via electronic media or on the paper MEOI Report Form. MEOIs that are identified from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anti-cancer therapy, whichever is earlier, need to be reported to the sponsor within 24 hours of the event in the same manner as outlined for SAEs (see Section 6.4.7.3).

Subjects should be assessed for the occurrence of possible MEOIs before administration of each dose of study treatment. Laboratory results should be evaluated, and subjects should be asked about any signs and symptoms experienced that are suggestive of an immune-related event. If laboratory test results or symptoms indicate possible immune-related MEOIs, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then the MEOI will be considered to be immune-related.

6.4.7.5 Definitions of Adverse Event

Adverse Event (AE)—Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, medical treatment, or procedure, and which does not necessarily have to have a causal relationship with this regimen. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, medical

treatment, or procedure whether or not considered possibly, probably, or definitely related to the medicinal product. Progression of cancer is not considered an AE unless it is considered to be drug-related by the investigator.

Treatment-Emergent Adverse Event (TEAE)—Any AE that occurs, or an existing condition that worsens in severity, after administration of the first dose of the study drug.

Medical Event of Interest (MEOI)—Selected non-serious AEs are classified as MEOIs. The following treatment-emergent immune-mediated event is an MEOI for CMB305:

- Pneumonitis

As NY-ESO-1 is only detected in certain testicular cells in healthy individuals (Gnjatic 2006), the following male genitourinary-related events are MEOIs for CMB305:

- Prostatic pain
- Groin pain
- Testicular pain
- Epididymo-orchitis

MEOIs for this study include the following:

- An overdose of the sponsor's investigational product that is not associated with clinical symptoms or abnormal laboratory results
- Results from protocol-specified or unscheduled laboratory results showing simultaneous:
    - Increased ALT and/or AST ≥3× ULN,
    - Increased serum total bilirubin ≥2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) and
    - No other reason can be found to explain the combination of increased aminotransferase enzymes and total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Note: These criteria are based upon available regulatory guidance documents. The purpose of these criteria is to specify a threshold of abnormal hepatic test results that may require an additional evaluation for an underlying etiology. The site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

During study conduct, additional new MEOIs may be identified by the Sponsor based on their clinical and laboratory features and understanding of underlying pathophysiology of the adverse events and will need to be reported as such. Such events may include dermatologic, endocrine, neurologic, gastrointestinal, respiratory and musculoskeletal toxicities, which are possibly

immune-mediated and possibly related to the study drug mechanism of action. Such adverse events may be delayed and wide ranging in terms of organs affected and severity.

Unexpected Adverse Event—An AE is "unexpected" when its nature (specificity), severity, or frequency are not consistent with the known or foreseeable risk of AE associated with the research procedures described in the protocol, Main Study ICF/assent form, or the Investigator Brochure.

Serious Adverse Event (SAE)—Any AE that results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization

  Note: Hospitalizations not to be reported as SAEs include admissions for planned medical/surgical procedure (such as scheduled tumor excision or debulking surgery) or routine health assessment requiring admission for baseline/trending of health status documentation (e.g., routine colonoscopy) or admission for social purposes such as lack of housing, economic inadequacy, caregiver respite, or family circumstances.

- A persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is a medically important condition that is judged by a health care professional as serious

The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event, and it does not refer to an event that hypothetically might have caused death if it were more severe.

Disability refers to a substantial disruption of a person's ability to conduct normal life function.

- Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. These may also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; or blood dyscrasias or convulsions that do not result in hospitalization. For reporting in this study, any suspected transmission of an infectious agent via an investigational medicinal product is considered a serious adverse event.

When there is doubt regarding an AE meeting the criteria for an SAE, the investigator should default to reporting the AE as an SAE.

There are special circumstances in which an SAE reporting form is used to communicate important clinical trial safety observations that may not constitute an SAE.

- Pregnancy: Although pregnancy is not considered an SAE and is instead a normal human experience, all pregnancies reported in female subjects occurring in the month before or month after or occurring in female partners of male subjects in the month before or 3 months after for the last investigational injection must be reported to sponsor.
- Overdose: An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. For reporting purposes, an overdose will be considered, regardless of adverse outcome, as an important medical event. All cases of overdose must be reported immediately to the sponsor.

6.4.7.6 Adverse Event Severity

All AEs will be evaluated according to the NCI-CTCAE v4.03 (2010) or newer (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf) For AEs not listed in this reference scale, severity will be assessed by the investigator according to the criteria in Table 5.

Table 5 Adverse Event Severity Assessment

Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 (Moderate)	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4 (Life threatening)	Life-threatening consequences; urgent intervention indicated
Grade 5 (Death)	Death related to AE

ADL = activities of daily living; AE = adverse event

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity of an AE should be documented to enable an assessment of the duration of the event at each level of intensity. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

6.4.7.7 Relationship

The investigator will report his or her interpretation of the relationship between an AE and the study treatment on the basis of their clinical judgment and the definitions in Table 6.

Table 6 Assessment of Relationship

Definitely related	AEs clearly attributable to study regimen administration
Probably related	AEs for which there is a reasonable possibility of causal association to study regimen
Possibly related	AEs for which there is confounding by comorbidities, medications or other considerations but for which it is not unreasonable that the AE may have been caused by study regimen. Note that it is not appropriate to invoke "you can't rule it out."
Not related	AEs that are considered clearly not causally related to study regimen, or for which there is a clear alternative explanation

AE = adverse event

If there is any question whether or not an AE is possibly, probably, or definitely related, the investigator should default to conservatism in categorization. Similarly, the investigator should default to conservatism by calling an AE an SAE if there is doubt regarding the serious nature of an AE, if it meets one of the definitions described above.

6.4.7.8 Clinical Laboratory Adverse Events

Clinically significant laboratory test results, in the opinion of the investigator, will be considered AEs and will be reported as shown in Section 6.4.7.

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in laboratory values within the normal range will require similar judgment. An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- An action on the study drug is made as a result of the abnormality
- Intervention for management of the abnormality is required
- At the discretion of the investigator should the abnormality be deemed clinically significant

6.4.8 Pregnancy

Sexually-active men and FCBP must use a highly effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before enrolling FCBP in this clinical trial, all FCBP must be advised of the importance of avoiding pregnancy during trial participation and for 30 days after the last dose of study drug administration and the potential risk factors for an unintentional pregnancy. Male subjects must be advised of the importance of their female partners avoiding pregnancy during the male subject's participation and for 3 months after the last dose of the study drug. All subjects (men and women) must sign an ICF documenting this discussion.

All FCBP must have a negative pregnancy test within 2 weeks prior to the study regimen initiation. If the pregnancy test is positive, the subject must not be enrolled in the study.

In addition, all FCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If following initiation of study dosing, it is subsequently discovered that a trial subject is pregnant or may have been pregnant within 1 month before or 4 months after, study regimens will be permanently discontinued, and the subject will be followed as possible by the investigator or designated health care professional to determine pregnancy outcomes for both mother and baby. If a male subject enrolled in study has a female sexual partner who becomes pregnant after initiation of the study, then the study subject should be asked by the investigator (or designated health care professional) for permission to approach his pregnant partner to follow-up to determine outcomes for both mother and baby.

6.4.9 HIV Screening Assessment

As part of study eligibility, subjects are required to have a negative HIV screening test at baseline. LV305 is an engineered lentivirus vector and is therefore derived from HIV. It is not known if treatment with LV305 will result in seroconversion of subjects to positive with HIV screening. Vectors derived from lentiviruses share some, but not all, of the proteins that are recognized in several screening blood tests for HIV. Secondary confirmatory assays such as Western Blot will demonstrate that the normal complement of HIV proteins is not present (unless, of course, the subject has developed true HIV infection). The informed consent document informs subjects regarding the possibility of positive HIV screening test after study treatment. Subjects enrolled in the study will be provided with a card from the study sponsor describing the possibility of a screening test becoming positive and the importance of confirmatory testing. In the event a study subject should have a screening HIV test performed and it returns a positive result, the site should inform and consult IMDZ for recommendations on the most appropriate confirmatory test to use.

6.4.10 Immune-mediated Events

While available data do not provide evidence of a causal relationship between CMB305 and the occurrence of immune-related events, a potential for such events exists because of the mechanism of action of CMB305. Investigators should promptly identify signs and symptoms of AEs representing an immunologic etiology and provide appropriate treatment. If an MEOI that is considered grade 2 or higher (with the exception of alopecia or vitiligo) occurs, subsequent doses of CMB305 should be withheld. CMB305 dosing should resume only after consultation with the sponsor.

The occurrence of any immune-mediated event will be evaluated by the data monitoring committee (DMC).

The immune-mediated event of pneumonitis will be captured as an MEOI; procedures for reporting MEOIs are provided in Section 6.4.7.4.

6.5 Removal of Subjects from the Trial or Study Drug

Unless consent is withdrawn and the subject is unwilling to continue with safety follow-up, the subject is lost to follow-up, or the study is terminated, all efforts should be made to continue tumor and quality of life assessments as well as safety monitoring of all subjects.

Subjects who withdraw prior to the end of the study should be followed for new AEs for at least until 30 days after their last dose of study drug, i.e., CMB305. If the subject withdraws prematurely and is unwilling to continue safety follow-up, any subsequent SAE that may be causally related to study drug (i.e., CMB305) that comes to the attention of the site staff should be reported to IMDZ.

Information for long-term survival status should be obtained by any means, which includes, but is not limited to, public records where allowed by local authority, telephone contact, during an in-clinic visit, chart review, or via communicating with an individual (e.g., family, friend, referring health care provider) who is knowledgeable of the subject's survival status. More frequent survival status updates may be obtained at the request of the sponsor.

6.5.1 Removal from Trial

While subjects will be encouraged to continue participation in the study for safety follow-up, subjects **MUST** be discontinued from the study for the following reasons:

1. Pregnancy within 1 month before or 4 months after study regimen administration (NOTE: All FCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant [e.g., missed or late menstrual period] at any time during study participation.)
2. Termination of the study for safety

3. Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness
4. Other

6.5.2 Removal from Study Drug

While subjects will be encouraged to continue participation in the study for safety and survival follow-up, subjects **MUST** be discontinued from receiving further study drug for the following reason:

- Progressive disease by RECIST v1.1 criteria
- Withdrawal of informed consent from study treatment
    - Subject will continue to be followed for imaging and quality-of-life assessment
- Any clinical AE that meets treatment discontinuation criteria in section 5.6 or any other reason that, in the opinion of the investigator, indicates that continued dosing on the study is not in the best interest of the subject
    - Subject will continue to be followed for imaging and quality-of-life assessment

Subjects will be permitted to continue study drug if the RECIST v1.1 criteria for PD are met provided they meet all the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor growth at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Subjects for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial apparent progression. Study treatment will be discontinued upon commencement of subsequent systemic anti-tumor therapy.

No unblinding will be permitted for subjects who continue study treatment beyond progression.

6.6 Appropriateness of Measurements

The measurements of efficacy and safety in this study are standard measurements widely used and generally recognized as reliable, accurate, and relevant. The safety measurements evaluated in this study are those used in most clinical studies, including the assessment of AEs.

7.0 PLANNED STATISTICAL METHODS

7.1 Determination of Sample Size

A total of 248 subjects will be randomly assigned in a 1:1 ratio such that 124 subjects will be included in each of the 2 treatment arms. The study is powered at 90% with 179 death events required to detect a HR of 0.59, which corresponds to a 41% reduction in the risk of death, and an approximately 69% increase in median survival compared with a placebo median survival of 20 months, and uses a 1-sided log-rank test, with an alpha of 0.0125, a 1:1 randomization ratio, and an interim OS non-binding futility analysis with boundary of HR = 1.0 at 67% of information time (120 death events from the 179 required death events for the final OS analysis). A total of 248 subjects will yield the 179 events required, under the assumption of 24 months for enrollment (25% of subjects enrolled in the first year and 75% of subjects enrolled in the second year) plus 42 additional months of follow-up.

With 141 PFS events, the study is powered at 90% to detect a HR of 0.55, which corresponds to a 45% reduction in the risk of PFS events (either disease progression or death), and an approximately 82% increase in median PFS compared with a placebo median PFS of 4 months, and uses a 1-sided log-rank test, with an alpha of 0.0125, and a 1:1 randomization ratio.

7.2 Analysis Sets

For the purpose of statistical analysis, there are 3 analysis sets: Intent-to-Treat set (ITT), Efficacy Evaluable set (EE), and Safety set.

- The ITT set consists of all subjects randomized. All analyses of this set will be based on the randomized treatment arm to which the subjects are assigned. Efficacy analyses performed in the ITT set will be considered to be the primary indicator of efficacy.
- The EE set consists of all subjects without major protocol violations, who have received at least 1 dose of study drug, and have the baseline and at least 1 post-baseline tumor assessments available. The EE set will be analyzed according to the treatment received. Efficacy analyses performed in the EE set will be considered to be supportive.
- The Safety set consists of all subjects taking any amount of study drug. The Safety set is the primary set for safety analyses including AEs and clinical laboratory data. Study treatment exposure also will be summarized using the Safety set. Efficacy analyses performed in the Safety set will be considered to be supportive.

7.3 Demographics and Baseline Characteristics

Subject disposition and characteristics including demographics, disease duration and stage at Screening, and relevant medical history will be summarized for the purpose of characterizing the subject population by treatment arm and establishing baseline comparability of the randomized treatment arms.

7.4 Primary Endpoints

- PFS, defined as the time from randomization to the investigator-determined (using RECIST v1.1) date of disease progression or death
- OS, as the time from randomization to the date of death

7.5 Secondary Endpoints

- TTNT
- DMFS
- ORR, defined by RECIST v1.1
- Safety and tolerability
- QoL, using the EQ-5D-5L for subjects ≥18 years of age or using the EQ-5D-Y for subjects 12 to <18 years of age

7.6 Exploratory Assessments or Analyses

- Intratumoral and peripheral blood anti-NY-ESO-1 immune changes

7.7 Efficacy Analysis

7.7.1 Primary Efficacy Analyses:

The 2 primary efficacy endpoints of PFS and OS will be compared between CMB305 and placebo. Overall survival is defined as the time from randomization to the date of death.

Progression-free survival by investigator's assessment is defined as the time from randomization to the investigator-determined (using RECIST v1.1) date of disease progression or death. Radiographic images will be collected and assessed using RECIST v1.1 until the time the subject begins a new line of treatment.

For the purpose of PFS analysis, any one of the following events, whichever occurs first, will be used:

- Disease progression per RECIST v1.1 (See Appendix 1 Table 7 [Eisenhauer 2009])
- Symptomatic deterioration (global health deterioration) as described by RECIST v1.1
- For subjects with NED at time of randomization, any new malignant lesion that occurs after randomization per RECIST v1.1 (See Appendix 1 Table 8)

Otherwise, subjects who do not have disease progression or have not died will be censored at the date when the last tumor imaging assessment determines a lack of progression. If a subject begins a new anti-cancer therapy or has radiotherapy, surgery, or other local regional therapy at a lesion site prior to documented progression, the subject will be censored at the last assessment where the subject was documented as progression free prior to the intervention. For subjects with NED at study entry, the appearance of a new malignant lesion as per RECIST v1.1 is defined as an event of progression for the purpose of PFS analysis. Subjects with 2 or more missing

response assessments (except for subjects with symptomatic deterioration) prior to a visit with documented progression (or death) will be censored at the last visit where the subject was documented to be progression free. PFS, by investigator's assessment, will be the primary PFS analysis. PFS by independent radiological review will be the supportive analysis.

The null hypothesis of no difference in OS/PFS between CMB305 and placebo, will be tested using a stratified log-rank test stratified by: disease status at screening (locally advanced unresectable versus metastatic), tumor response during screening (PR/SD versus CR/ NED), and by baseline presence of anti-NY-ESO-1 antibody (yes versus no)).

The null hypothesis will be rejected, and it will be concluded that OS/PFS on CMB305 is superior to that on placebo in subjects with synovial sarcoma if the 1-sided p value at the final analysis for the stratified log-rank test is less than the pre-specified alpha of 0.0125 as discussed in Section 7.10, Multiplicity. The associated HR and its 2-sided 97.5% and 95% CI will be provided using the stratified Cox proportional hazard model. The Kaplan-Meier curve will summarize OS/PFS graphically by treatment arm. Tabular summaries of the Kaplan-Meier curves, including the median, will be provided by treatment. The 1-year and 18-month OS/PFS rate will be provided by treatment. The final PFS analysis will be conducted when a total of 141 PFS events occur. The final OS analysis will be conducted when a total of 179 deaths occur.

A pre-planned sensitivity analysis will be performed based on the number of cycles and type of prior therapy (neoadjuvant/adjuvant chemotherapy and surgery and/or radiotherapy).

7.7.2 Secondary Efficacy Analyses:

The secondary efficacy endpoints of TTNT, DMFS, ORR and QoL using the EQ-5D-5L or EQ-5D-Y will be compared between treatment arms.

The secondary efficacy endpoints will only be evaluated if at least one of the primary efficacy endpoints demonstrates superiority for CMB305 over placebo. Furthermore, to control the overall family-wise type I error rate at 1-sided $\alpha = 0.025$ for the secondary efficacy endpoints, the secondary efficacy endpoint of TTNT will be tested first at 1-sided alpha of 0.025. DMFS will be tested at 1-sided alpha of 0.025 only if TTNT shows significant improvement.

7.7.2.1 Time to Next Treatment

Time to next treatment is defined as the time from randomization to start of post-study treatment anti-cancer therapy. Subjects who do not start post-study treatment anti-cancer therapy will be censored at their last known date of being alive. TTNT will be analyzed using the same methods described for OS/PFS. In the event that the percent of subjects with competing events in either arm exceeds 3%, the cumulative incidence estimates, and Gray's test will be the main TTNT comparison between the treatment arms.

7.7.2.2 Distant Metastasis-Free Survival

Distant metastasis-free survival is defined as the time from randomization to evidence of a new distant metastasis not documented at time of randomization. DMFS will be analyzed using the same methods described for OS/PFS. In the event that the percent of subjects with competing events in either arm exceeds 3%, the cumulative incidence estimates, and Gray's test will be the main DMFS comparison between the treatment arms.

7.7.2.3 Other Secondary Efficacy Endpoints

ORR defined by RECIST v1.1 will be summarized by the number and percent of subjects who achieve a CR or PR based on the investigator's assessment. ORR will be compared between treatment arms using a logistic regression.

QoL (EQ-5D-5L or EQ-5D-Y) scores will be compared between the treatment arms using a mixed model.

7.8 Safety Analysis

Safety will be assessed primarily based on reported AEs. A TEAE is an AE with an onset on or after the initiation of study treatment, or a pre-existing condition that worsens after initiation of study treatment (i.e., increase in severity). Medical events of interest, immune-mediated events, and AEs that occur more than 30 days after the last dose, and that are deemed as related to the study drug, will be included as TEAEs. TEAEs occurring from the time of the first dose through 30 days after the last dose of the study drug and medical events of interest, immune-mediated events and related AEs will be summarized. All AEs will be coded using the Medical Dictionary for Regulatory Affairs® (MedDRA v20.0 or newer). TEAEs will be tabulated by system organ class, preferred term, by treatment, and will be further categorized by NCI-CTCAE (v4.03 or newer) grade, and by relationship to the study drug. Clinically significant laboratory abnormalities, as measured by either the local or central laboratory, will be reported as AEs. The incidence for each AE will be provided as the total number of subjects that experience the AE, as well as the percentage of the population that this represents. If an AE is reported more than once during treatment for a given subject, the worst grade of severity and the most conservative relationship will be presented in the summary tables.

AEs will also be listed for individual subjects, along with information regarding onset, duration, grade, relationship to the study drug, and outcome. AEs that lead to withdrawal from the study treatment will be listed and summarized. Tabulations and listings of SAEs and deaths also will be generated.

Treatment exposure will be provided by treatment arm. The number of CMB305 or placebo injections, duration of exposure, and number of subjects with dose reductions/interruptions will be summarized by treatment arm based on the Safety set.

Laboratory values measured by the central laboratory will be used in the analysis of laboratory toxicities and will be defined based on universal normal ranges and NCI-CTCAE, Version 4.03 or newer. The number and percentage of subjects will be summarized by grade using the most severe grade by treatment arm. Clinically significant changes in laboratory values will be summarized by treatment arm. Laboratory values will be listed, with grade 3 or 4 values flagged.

All concomitant medications and prior medications will be coded to therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Classification. The incidence of prior and concomitant medication usage will be summarized by treatment arm, by therapeutic drug class, and generic drug names.

7.9 Exploratory Analysis

The baseline anti-NY-ESO-1 immune response and histologic and molecular changes in peripheral blood and tumor tissue and their association with clinical outcomes will be explored. In addition, a relationship between an induced anti-NY-ESO-1 immune response as well as tumor tissue changes during study treatment and clinical outcomes will be evaluated using peripheral blood and tumor tissue biopsies collected during study treatment at select sites.

7.10 Multiplicity

The study is to be conducted with PFS and OS as 2 primary endpoints with the goal of a regulatory approval based on PFS or OS. The overall type I error probability is specified to be 1-sided 0.025 with success for either of the 2 primary endpoints defining study success using the Bonferroni method to specify that each endpoint will be evaluated using a type I error probability of 1-sided 0.0125 in order to protect the overall type I error.

7.11 Data Monitoring Committee and Interim Analysis

A data monitoring committee will be established with the responsibility of safeguarding the interest of study subjects and maintaining the overall integrity of the study. The DMC will review safety data periodically during the study as described under Section 8.17 (Data Monitoring Committee) of this protocol and will evaluate the results of final PFS analysis and a planned interim OS analysis to assess futility with the possibility of a recommendation for stopping the study early because of futility. The OS non-binding futility boundary is set to be HR = 1.0. It will be conducted at 67% of information time (120th death event from the 179 required death events for final OS analysis). If deemed necessary by the DMC, unblinded data may be reviewed on a case-by-case basis. The sponsor will remain blinded to study treatment until either 1 of the 2 primary endpoints is met or until the study has been stopped early. Details of DMC function will be governed by a DMC Charter developed by the sponsor and accepted by DMC members.

8.0 ADMINISTRATIVE CONSIDERATIONS

8.1 List of Personnel and Organizations Responsible for Conduct of the Study

A list of personnel and organizations responsible for the conduct of the study will be provided to the study sites as part of the Investigator Study File (or equivalent). This list will be updated by the IMDZ or its authorized representatives and provided to study sites on as-needed basis.

8.2 Trial Sponsor:

Immune Design Corp. (IMDZ)
1616 Eastlake Ave. E, Suite 310
Seattle, WA 98102 USA

8.3 Sponsor's Medical Monitor:

PPD

Immune Design Corp. (IMDZ)
601 Gateway Blvd., Suite 250
South San Francisco, CA 94080 USA
Office: PPD
Email: PPD

8.4 Clinical Trial Agreement

This study will be conducted under a Clinical Trial Agreement between IMDZ (or its authorized representatives) and the respective institutions representing the study sites. Any financial support given to the study sites will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement, which must be signed before the start of any study related procedures, will clearly delineate the responsibilities and obligations of the investigator and the sponsor (or its authorized representatives), and will form the contractual basis upon which the study will be conducted.

8.5 Financial Disclosure by the Investigator

Prior to study initiation, the investigator and any subinvestigator(s) directly involved in the treatment or evaluation of study subjects at each study site will disclose to IMDZ (or its authorized representatives) any relevant financial or proprietary interests in either the study product or the sponsor company. The appropriate disclosure form(s) will be provided by the sponsor (or its authorized representatives) for this purpose. Any relevant updates to the financial disclosure information that occur during the conduct of the study, or during one year after completion of the study, will be provided by the investigator and subinvestigator(s) to the sponsor (or its authorized representatives). All financial disclosure information provided by the investigator and subinvestigator(s) will be submitted to appropriate competent authorities according to the applicable regulatory requirements.

8.6 Clinical Study Registration and Results Disclosure

IMDZ will provide the relevant study protocol information in a public database (ClinicalTrials.gov) before or at commencement of the study, as required by the 2007 FDA Amendments Act. IMDZ (or its authorized representatives) may also provide study information for inclusion in national registries according to local regulatory requirements.

If a potential subject contacts the sponsor (or its authorized representatives) regarding participation in the study, the investigator agrees that the sponsor (or its authorized representatives) may forward the relevant study site and contact details to the subject. Based on the inclusion and exclusion criteria for the study, the investigator will assess the suitability of the subject for enrollment into the study. Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record on ClinicalTrials.gov.

8.7 Institutional Review Board or Independent Ethics Committee Approval

The protocol and the ICFs and assents must have the approval of a properly constituted IRB/IEC responsible for approving clinical studies. The signed IRB/IEC approval letter must specify the date of protocol and ICF approval and identify the documents approved including the investigator's name, the protocol version, date, and title. Any subject materials or advertisements used to recruit volunteers should also be reviewed and approved by the IRB/IEC.

Study drug supplies will not be shipped to the site until a signed approval letter from the IRB/IEC has been received as well as approval from the local competent authority(ies) and a clinical trial agreement has been signed by IMDZ or its authorized representative and the clinical site.

8.8 Ethical Conduct of the Study

All investigators on the protocol must have received formal training in the ethical conduct of human research. The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. All eCRFs, compliance with the protocol, compliance with GCP, and compliance with FDA regulations will be monitored by an IMDZ monitor or designee as outlined in the study's Clinical Monitoring Plan Document.

8.9 Subject Information, Consent, and Assent

As specified in ICH, GCP and the US 21 CFR Section 50.25, the informed consent discussion must emphasize that participation in the study is voluntary and that subjects have the right to withdraw their consent at any time without giving a reason and without any disadvantage for their subsequent care.

Written informed consent or assent must be obtained from the subject prior to performing any study-related procedures, including Pre-screening or Screening assessments. The investigator or investigator's designee will provide background information on the study, including the benefits and risks of the investigative regimen. The investigator or investigator's designee will also encourage the prospective subject to ask questions about the study and will provide the prospective subject with sufficient opportunity to consider whether or not to participate.

Verification of the signed ICF or assent will be recorded in the subject's eCRF. The original signed ICFs and assents will be filed with the subject's records and/or in the Investigator Study File (or equivalent). A copy of the signed consent or assent must also be provided to the subject, and, if the subject is under 18 years of age, to the subject's legal guardian.

The subject ICF and assent templates that have been provided for this study may be revised by an investigator or an IRB/IEC based on the local requirements. However, all changes requested by an investigator or an IRB/IEC, even those that are not substantial and/or do not affect the rights, safety or welfare of a subject, must be approved by IMDZ or its designee.

The subject ICF and assent must be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revision of these documents must be approved by the IEC/IRB before they can be used in the study. Subjects must be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue participation in the study. The communication of this information should be documented by having all parties concerned sign and personally date the revised ICF or assent.

8.9.1 Assent for Subjects Under the Age of Consent (Pediatric Subjects)

For all subjects who are under the age of consent (i.e., pediatric subjects under 18 years of age); the written informed consent of a legally acceptable representative is required. Pediatric subjects who can understand the nature, scope, and possible consequences of the study must also give their assent in writing via the assent document, as appropriate, and per local or institutional requirements.

8.10 Subject Confidentiality

All study documents, including the study protocol and eCRFs, are the confidential property of IMDZ and should be treated as such.

All subjects screened for the study will be documented in a screening log in compliance with the requirements of individual study sites. Subjects not enrolled into the study will be documented as such in the screening log together with the reason for not having been enrolled.

The investigator will maintain a personal list of subject names and subject numbers (Subject Identification List) for participants in the study to enable records to be identified at a later date. These records should be retained in a confidential manner for the duration stipulated by applicable regulatory requirements. Subject names shall not be revealed to IMDZ or its

authorized representative. Only the subject identifier will be recorded in the eCRF, and if the subject's name appears on any other document, it must be redacted and replaced with the subject identifier before a copy of the document is supplied to IMDZ or its authorized representatives. Clinical sites will comply with local laws regarding anonymization of subject identifiers, as required. In the event of accidental communication of subject names or other inappropriate identifying information, immediate steps to redact the information from all study files will be implemented, with appropriate documentation in the subject study file.

The ICF will include a statement that all study findings, irrespective of the medium on which they are stored, will be handled in strictest confidence in accordance with applicable data protection laws (e.g., the European Data Protection Directive [95/46/EC] and the US Health Insurance Portability and Accountability Act [HIPAA]), and will be evaluated by the sponsor and/or a competent regulatory authority in an anonymized form. The subjects are also to be informed that their medical records may be audited or inspected by qualified delegates from the sponsor or a competent regulatory authority. The subject's written consent authorizing direct access to his medical records, and computer processing and publishing of his anonymous personal data, must be obtained prior to participation in the study.

8.11 Quality Control and Assurance

IMDZ performs quality assurance checks on all clinical studies that it sponsors. Before the enrollment of any subject in this study, IMDZ (or its authorized representative) and the investigator will review the protocol, the Investigator Brochure, the eCRFs and instructions for completing them, the procedure for obtaining informed consent or assent, and the procedure for reporting AEs/SAEs. Site monitoring visits will be performed by IMDZ (or its authorized representative) on a regular basis pursuant to its monitoring plan. During these visits, information recorded on the eCRFs will be verified against source documents. After the eCRFs are received by IMDZ (or its authorized representative), they will be reviewed for safety information, legibility, completeness, accuracy, and logical consistency. The data will be entered into a database. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors may be used to help monitor the study. As necessary, requests for clarification or correction will be sent to the investigator.

Data entered in the eCRF will be source verified for accuracy and completeness. In addition, protocol compliance and compliance with FDA regulations and ICH GCP guidelines will be verified.

8.12 Study Files and Materials

Before the start of any study-related procedures, all essential documents specified by ICH GCP and other applicable regulations must be available in the relevant files maintained by IMDZ (or its authorized representatives) and the investigator. An Investigator Study File prepared by the sponsor (or its authorized representatives), containing all applicable documents for use at the study site, will be made available to the investigator before the start of the study. A list of

personnel and organizations responsible for conduct of the study as well as the list of investigators will be included in the Investigator Study File. The respective files will be kept and updated by the sponsor (or its authorized representatives) and the investigator, as applicable.

All study documentation and materials maintained in the Investigator Study File at the study site must be available for inspection by the sponsor's study monitor (or its authorized representatives) to determine that all required documentation is present and correct (see Section 8.15).

The study may be audited or inspected by an authorized representative from IMDZ or a competent regulatory authority (see Section 8.15).

8.13 Monitoring of the Study

The investigator at each site will allow the sponsor's study monitor (or its authorized representatives) reasonable access to the eCRFs and direct access to related source documents for monitoring purposes as frequently as the sponsor deems necessary. These documents include records of tests performed as a requirement for participating in the study as well as other medical records required to confirm information contained in the eCRF, such as past medical history and secondary diagnoses.

Before each monitoring visit, the investigator (or its authorized representatives) should record all data generated since the last monitoring visit in the eCRF. The investigator and other relevant personnel at each study site will be expected to cooperate with the sponsor's study monitor to assist in providing any missing information.

The study monitor will require access to the Investigator Study File to ensure completeness of all documentation required for the study. The study monitor will ensure that the investigator at each site has been provided with adequate means for organization and filing of study documentation.

The date on which the study monitor (or its authorized representatives) visits the study site will be recorded in the Site Visit Log. During monitoring visits, the study site's coordinator (if applicable) and the investigator should be available, the source documentation should be accessible, and a suitable environment should be provided for the study monitor to review study related documentation.

The main objectives of monitoring visits conducted by the study monitor include:

- Resolution of any problems
- Examination of all study documentation for completion, adherence to the study protocol, and possible AEs
- Clarification of inconsistencies or missing data
- Verification of study data against source documents
- Checks that investigator obligations have been fulfilled

- Review of ICFs and dates of consent/assent
- Inspection of drug product with respect to storage, labeling, and documentation
- Drug accountability

After each subject's visit to the study site, the investigator (or its authorized representatives) will ensure that all data have been entered into the eCRF correctly and in a timely manner, after which the investigator will sign the eCRF.

8.14 Protocol Amendments

A "substantial" amendment of a study protocol is any written description of change(s) to, or formal clarification of, a study protocol that may have a significant impact on the safety or physical or mental integrity of subjects, the scientific value of the study, the conduct or management of the study, or the quality or safety of any drug product used in the study. The IRB/IEC must approve all substantial protocol amendments prior to their implementation. If required by applicable local regulatory requirements, the local regulatory authority must also approve all substantial protocol amendments prior to their implementation.

A "non-substantial" amendment of a study protocol includes minor corrections or clarifications that have no significant impact on the way the study is to be conducted and has no effect on the safety of participating subjects (e.g., change in study monitor, contact details). If required by applicable local regulatory requirements, the IRB/IEC, and/or the local regulatory authority should be notified of all non-substantial protocol amendments. The substantial and non-substantial protocol amendments will be integrated into an updated study protocol at the discretion of the sponsor if the changes to the original study protocol are numerous, or if required by applicable regulatory requirements.

8.15 Audits and Inspections

The study may be audited or inspected by authorized representatives from IMDZ or a competent regulatory authority. In the event of an audit by the sponsor, the investigator must make all study-related documentation available to the auditor(s). Regulatory authorities may request access to all study related documentation, including source documents, for inspection and copying in keeping with applicable regulations. The sponsor will immediately notify the investigator (or vice versa) of an upcoming audit or inspection.

If an audit or inspection occurs, the investigator and relevant personnel at the study site must allocate sufficient time to discuss the findings and any relevant issues.

8.16 Electronic Case Report Forms and Study Records

The investigator is responsible for maintaining adequate and accurate medical records from which information will be transferred into the study electronic data capture (EDC) system. The eCRFs should be completed by a trained study team member at the investigative site.

An eCRF will be provided for each subject. No data will be recorded directly on the eCRF without additional source documentation. Data/corrections entered will be signed or initialed by the study personnel undertaking that procedure.

Only complete eCRFs, reviewed and signed by the investigator indicating his/her assurance of the accuracy of all recorded data, will be accepted. It is expected that the investigator and his/her staff will cooperate with the monitoring team and provide any missing data in a timely manner.

Information on the eCRF will be verifiable to source documents. Other records that will be considered source documents include, but are not limited to, hospital records, clinic charts, radiographic data, laboratory reports, and pathology reports. Copies of source documents that should be sent to IMDZ or its authorized representative, if requested, include hospital or clinic records, radiographic data, laboratory reports, pathology reports, operative summaries, and discharge reports. Other source documents may include hospital discharge summaries, if available, or information in lieu of a discharge summary, such as discharge orders or progress notes; any relevant notes pertaining to AEs, additional surgical procedures, or deaths and autopsy reports. Any documentation sent from the site should be redacted to exclude subject identifying information.

8.17 Data Monitoring Committee

A DMC will be established to provide independent review of safety data and to assure that the risk to subjects is minimized, in addition to the 2 interim efficacy analyses described under Section 7.11 (Data Monitoring Committee and Interim Analysis) of this protocol. The DMC will review all related and unexpected (i.e., expedited) SAEs as individual cases arise and will perform periodic reviews of all AEs, laboratory results, and subject discontinuations. If deemed necessary by the DMC, unblinded data may be reviewed on a case-by-case basis.

Safety data will be collected and monitored on an ongoing basis throughout the study. IMDZ will summarize all available safety and laboratory data on all subjects at regular intervals (approximately every 3 months for the first 50 subjects, then approximately every 6 months) during the study, as specified in the DMC charter. IMDZ and the DMC will conduct separate reviews of these data for any safety trends that might impact the treatment of subjects.

The DMC may convene on an ad-hoc basis to evaluate any urgent safety issues. Upon request, the DMC will be granted access to any available data pertinent to the issues under evaluation. An independent DMC Service Group will provide cumulative data, as specified in the DMC charter, to the DMC for review, including clinical laboratory values, AEs, SAEs, MEOIs, and subject discontinuations.

8.18 Protocol Compliance

The investigator must conduct the study in compliance with this study protocol as agreed to by the sponsor and approved by the regional competent regulatory authority(ies) and IRB/IEC, per local requirements.

The investigator should not implement any deviation from, or changes to, the study protocol without agreement by IMDZ (or its authorized representatives) and documented approval or favorable opinion from the IRB/IEC of an amendment to the study protocol. Exceptions include only cases of medical emergency to address immediate hazards to study subjects. No protocol waivers will be granted by the sponsor.

In the event of a medical emergency, the investigator at each site may institute any medical procedures deemed appropriate to address an immediate hazard to a subject without prior IEC/IRB approval or favorable opinion. As soon as possible, the implemented deviation and reason for the deviation should be submitted to:

- IMDZ (or its authorized representatives) for agreement
- The IRB/IEC for review and approval or favorable opinion (if required)
- The applicable competent regulatory authority (if required)

Details of the procedure for implementing study protocol amendments are available in Section 8.14.

At the earliest opportunity, the investigator (or its authorized representatives) must inform IMDZ (or its authorized representatives) about any notable protocol deviations and explain any deviation from the approved study protocol in the eCRF and/or in the Protocol Deviation Log, if applicable.

8.19 Retention of Data

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with IMDZ. It is the responsibility of IMDZ to inform the investigator/institution as to when these documents no longer need to be retained.

8.20 Clinical Study Report

After completion of the study, a clinical study report covering clinical and statistical aspects of the study will be prepared by IMDZ (or its authorized representatives) in consultation with the lead investigators. As required by the applicable regulatory requirements, the clinical study

report will be signed by the sponsor's responsible medical officer as well as the lead investigators (if applicable).

Progress reports and/or a summary of the clinical study report will be provided to the IRB/IEC and competent regulatory authorities in accordance with applicable requirements.

8.21 Publication and Disclosure Policy

The rights and obligations of investigators and the sponsor concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Agreement for the study (see Section 8.4).

It is expected that the results of this study will be published in a peer-reviewed journal. A publication plan for the primary results will be discussed with the investigators and established before the start of the trial. IMDZ will have 30 days from the date of receipt for review and shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that the sponsor's confidential and proprietary data, in addition to the sponsor's intellectual property rights, are protected. Any manuscripts reporting the results of this clinical trial must be provided to the sponsor by the principal investigator for review and comment prior to submission for publication. Abstracts, press releases, and other media presentations must also be forwarded to the sponsor prior to release. No publication, manuscript, or other form of public disclosure shall contain any of the sponsor's confidential/ proprietary information. Co-authorship of subsequent publications with IMDZ personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

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APPENDIX 1: DETERMINATION OF TUMOR RESPONSE

Tumor response will be determined using RECIST v1.1 (Table 7) for subjects who enroll in the study with evidence of target and/or non-target lesions (Eisenhauer 2009). For subjects with NED at study entry RECIST v1.1 will be used such that the appearance of any new malignant lesion will be defined as PD, and no new lesions will be defined as SD as outlined in Table 8. Subjects with symptomatic deterioration will be documented as having had an event of PD as of the date the symptomatic deterioration was determined by the investigator.

Table 7 Time Point Response: Subjects with Target (+/- non-target) Disease

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Non-evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR – completed response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable

Table 8 Disease Response Assessment on Study for Subjects with no Evidence of Disease at Study Day 1

Baseline		Post Day 1 Response Assessment			Overall Response
Target lesion	Non-Target lesion	Target lesion	Non-Target lesion	New Lesions	
Absent	Absent	Any	Any	New	PD
Absent	Absent	Absent	Absent	None	SD

PD = progressive disease; SD = stable disease

APPENDIX 2: ECOG

ECOG PERFORMANCE STATUS[a]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

[a] As published in American Journal of Clinical Oncology: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX 3: EUROQOL 5-DIMENSION 5-LEVEL

For subjects ≥18 years of age:

https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

APPENDIX 4: EUROQOL 5-DIMENSION-YOUTH

For subjects 12 to <18 years of age:

https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-Y_User_Guide_v1.0_2014.pdf

APPENDIX 5: Study Flow Diagrams for Subjects Receiving 4-cycles, 6-cycles and 8-cycles of First-line Systemic Anti-Cancer Therapy or Local Regional Therapy.

Figure 4 Study Flow Diagram for Subjects Receiving 4-Cycles of First-Line Systemic Anti-Cancer Therapy

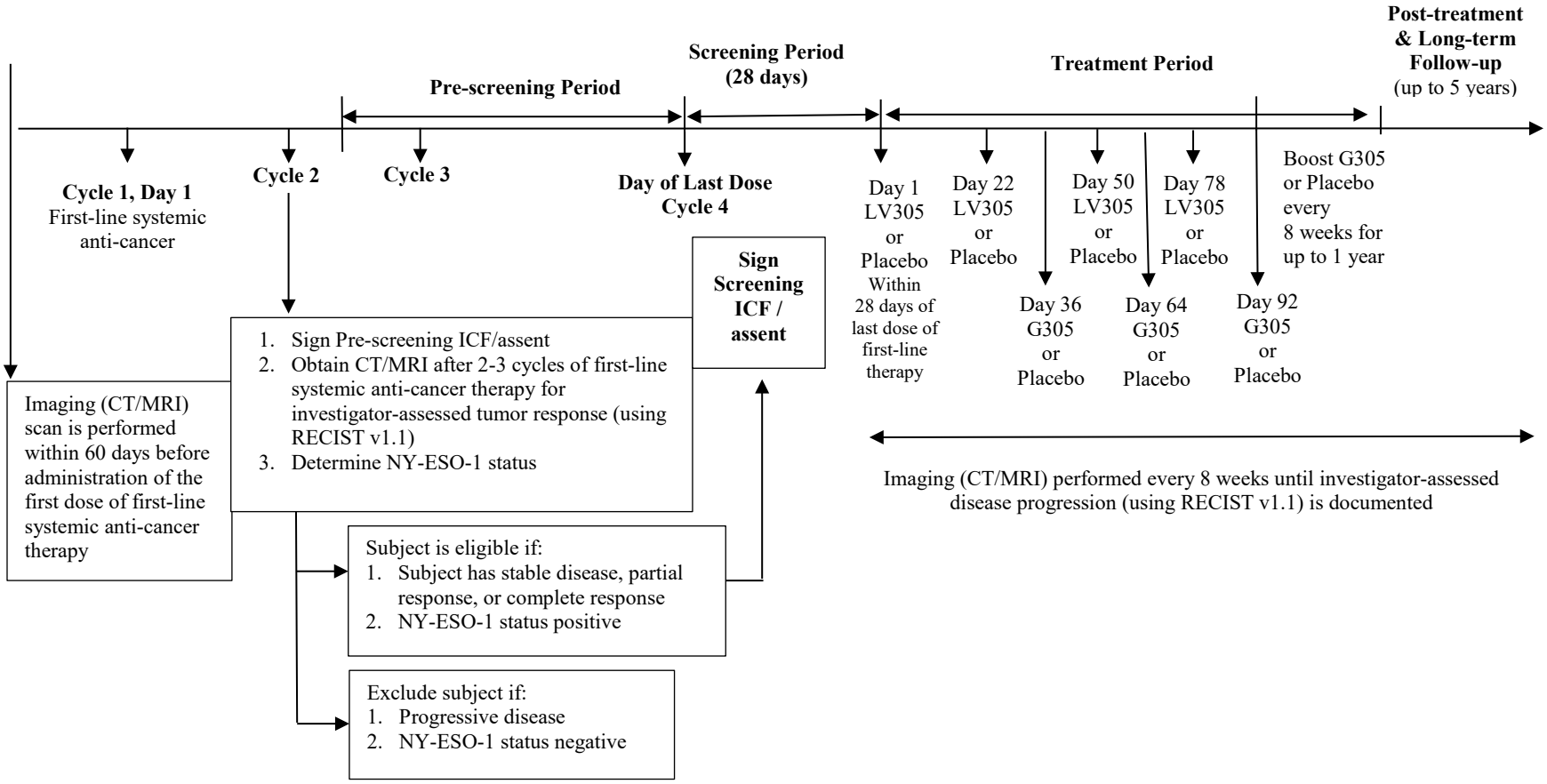

Figure 5 Study Flow Diagram for Subjects Receiving 6-Cycles of First-Line Systemic Anti-Cancer Therapy

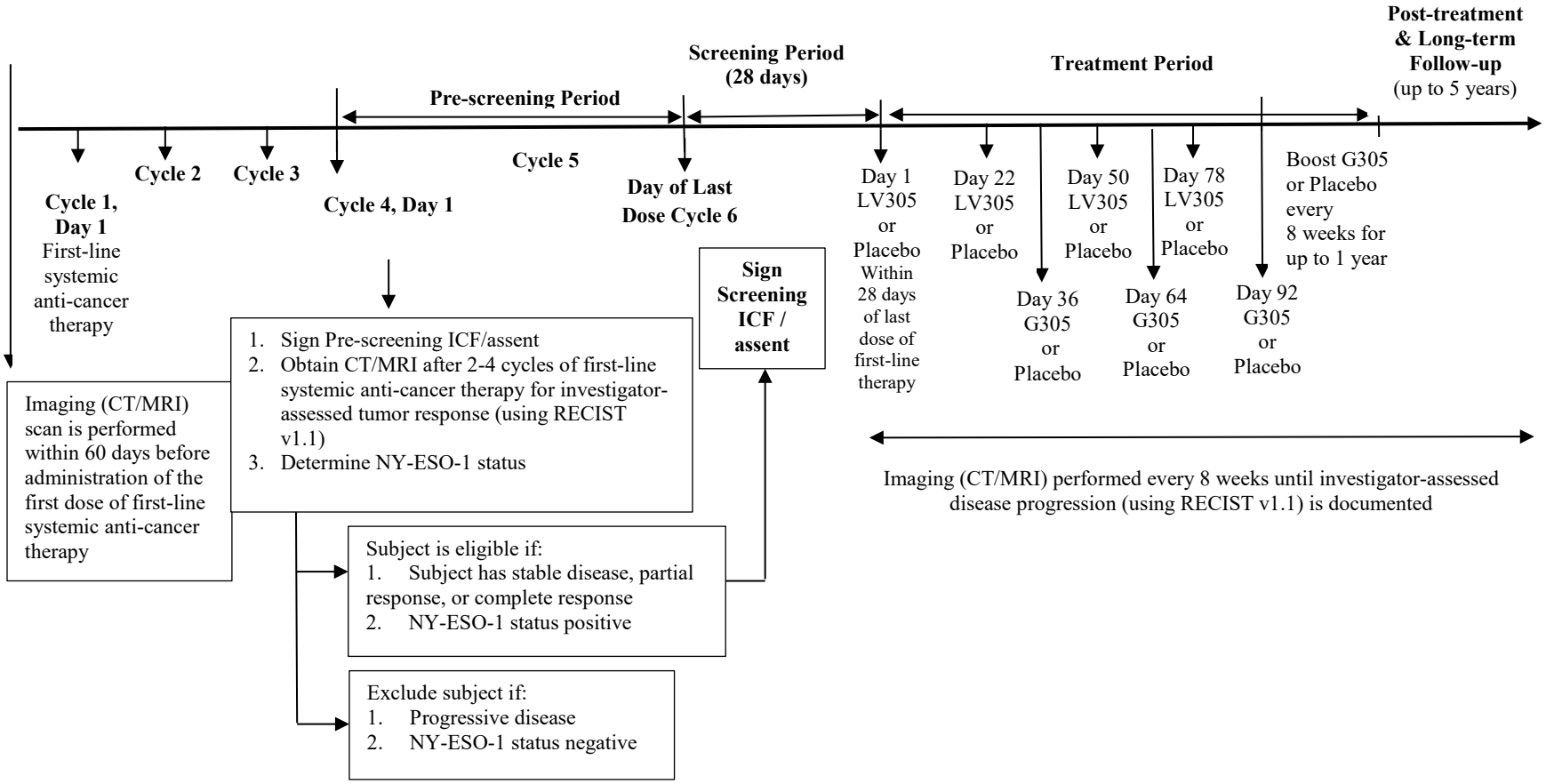

Figure 6 Study Flow Diagram for Subjects Receiving 8-Cycles of First-Line Systemic Anti-Cancer Therapy

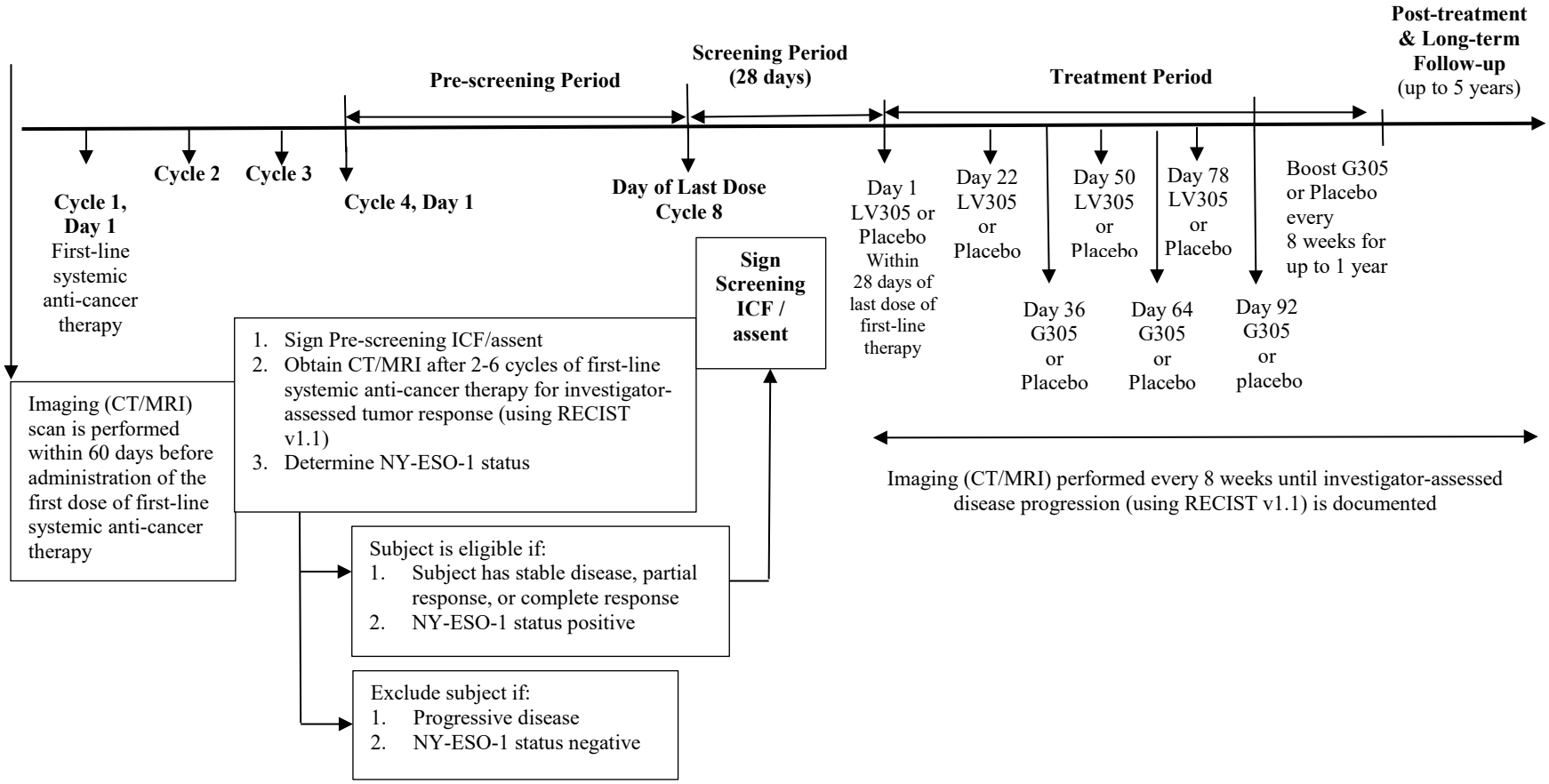

Figure 7 Study Flow Diagram for Subjects Receiving Local Regional Therapy